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Lack of association between C282Y and H63D polymorphisms in the hemochromatosis gene and risk of multiple sclerosis: A meta-analysis

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Abstract. Increasing evidence supports the potential role of iron metabolism in multiple sclerosis (MS). Previous studies examining the association between polymorphisms of the hemochromatosis gene (*HFE*) and susceptibility to MS have yielded inconsistent results. In the present study, a meta-analysis of 7 studies was performed conducted in populations of Caucasian origin using the Comprehensive Meta-analysis 3.0 software. The strength of association between the C282Y and H63D polymorphisms in *HFE* and MS risk was estimated by odds ratios with 95% confidence intervals. Cochran's Q statistic and I^2 tests were applied to quantify heterogeneity between studies. An Egger's test was used to estimate publication bias. The C282Y and H63D polymorphisms had no significant association with increased MS risk (all P≥0.05) in the following genetic comparison models: Dominant model (YY + CY vs. CC or DD + HD vs. HH) and allele contrast (Y vs. C or D vs. H). No apparent publication bias or significant heterogeneity was found between studies. These results suggest that the *HFE* polymorphisms C282Y and H63D are not associated with susceptibility to MS in populations of Caucasian origin. Further studies should be performed in a larger series of MS patients to evaluate the contribution of *HFE* and other genetic variants associated with iron regulation in the development and progression of MS.

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Abbreviations: β2M, β-2-microglobulin; *HFE*, hemochromatosis gene (human); CI, confidence interval; MS, multiple sclerosis; OR, odds ratio

Key words: HFE, multiple sclerosis, C282Y, H63D, iron, meta-analysis

Introduction

Multiple sclerosis (MS) is a neurodegenerative disease of the central nervous system with autoimmune and inflammatory features. The etiology of MS remains unclear despite extensive research over the past five decades. It is generally hypothesized to be a multifactorial entity arising from complex interactions between genetic predispositions, infectious exposures and factors leading to pro-inflammatory conditions, such as smoking, obesity and deficiency of vitamin D (1-4).

A growing body of evidence supports a possible role of iron metabolism in a number of diseases with a neurodegenerative component, including MS (5,6). Several post-mortem studies and studies using conventional and the new iron-sensitive imaging techniques have described changes in brain iron homeostasis, linking iron deposition in different brain regions to the demyelinating process in MS patients (7-11). A recent study in MS patients found an association between the serum iron concentration and evidence of increased iron deposition in deep gray matter subcortical structures (12). In addition, in our previous study in experimental autoimmune encephalomyelitis, the most commonly used animal model of MS, it was found that chronic iron overload influenced the clinical course of the disease in Dark Agouti rats; it affected disease progression and mortality, with milder effects on female rats (13). The human hemochromatosis gene (*HFE*) is an important regulator of cellular iron homeostasis and has the highest prevalence of polymorphisms amongst the iron regulatory genes known to alter brain iron levels and structure. In *HFE*, the single nucleotide polymorphisms C282Y and H63D can result in phenotypes with altered iron parameters. Homozygosity or compound heterozygosity for the C282Y and H63D variants can lead to iron overload and the disorder known as hereditary hemochromatosis.

Since HFE also acts as a signal peptide, it has two domains (α1 and α2) that form an extracellular transferrin receptor-binding region and an immunoglobulin-like domain (α3) (14,15). Cysteine 282 is essential for the binding of β-2-microglobulin (β2M) to the α3 domain and for the extracellular presentation of HFE. When HFE binds to β2M, it

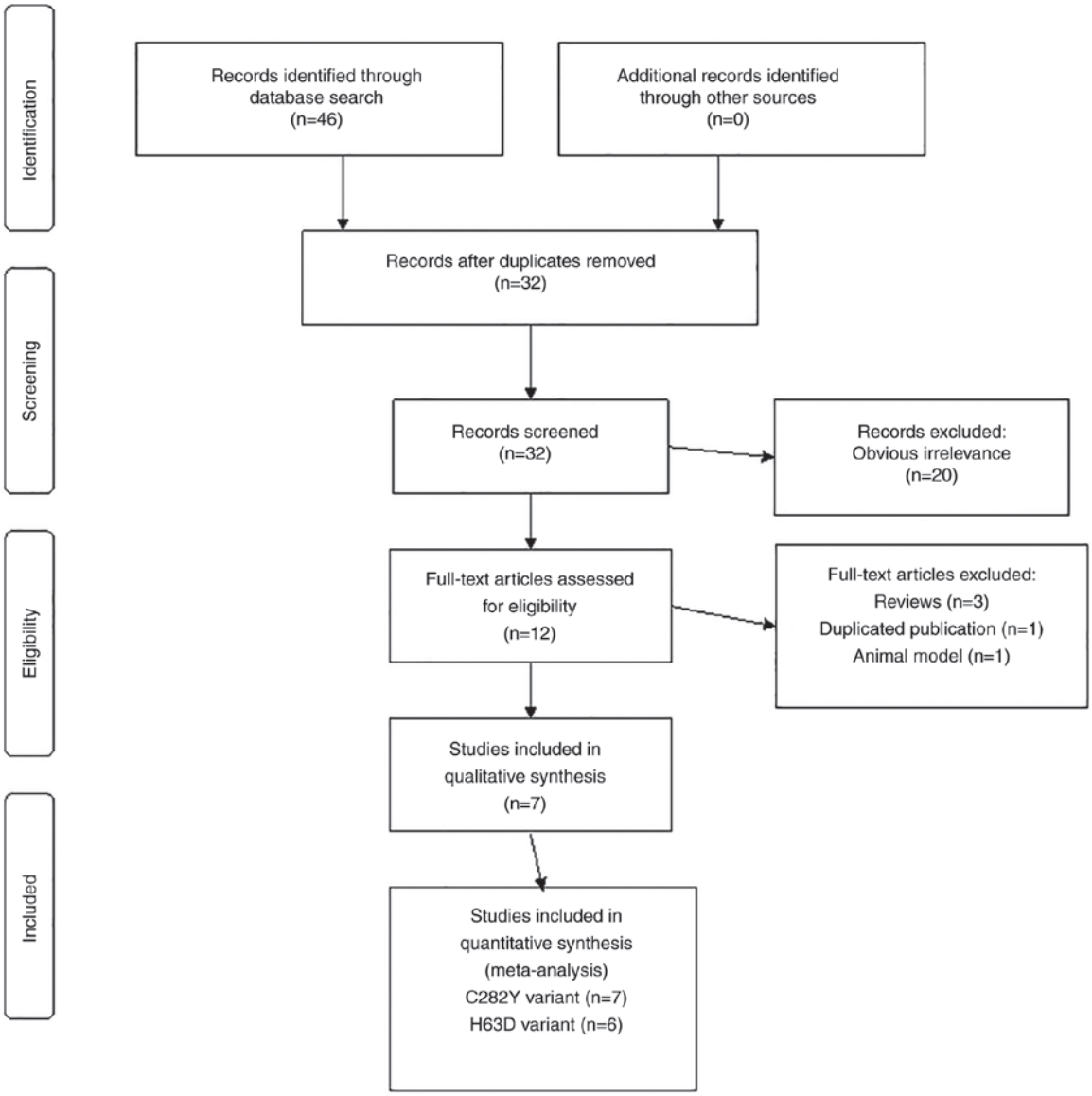

Figure 1. Flow chart of study selection.

forms a heterodimer expressed at the cell surface (16). In the case of C282Y mutation, the disulfide bond in the α3 domain is disrupted, thus β2M cannot bind and HFE is not present at the cell surface, but instead aggregates in the cytoplasm (17). It was confirmed that when *HFE* C282Y is overexpressed, the binding capacity of HFE and TFR is significantly reduced (16). Therefore, C282Y homozygosity results in higher serum iron and ferritin levels and an increase in transferrin saturation (18). Histidine 63 forms a salt bridge in the transferrin receptor-binding region (19). The H63D mutation disrupts the salt bridge and alters the tertiary structure of HFE and its function (17).

Animal models have also been used to improve our understanding of the role of the C282Y and H63D polymorphisms. For example, *Hfe* knockout mice, homozygous for the deletion corresponding to the α1 and α2 domains of HFE, showed increased iron absorption and plasma concentration, as well as increased transferrin saturation and iron overload. Homozygosity for the C282Y mutation also caused iron overload (20).

The few studies investigating the association between the C282Y and H63D polymorphisms and the risk of MS have reported inconclusive results (21-27). As a single study typically has a relatively small number of participants with low statistical power, a meta-analysis may be an appropriate approach for obtaining a more definitive conclusion. Therefore, a meta-analysis of 7 studies conducted in different populations of Caucasian origin was performed. To the best of our knowledge, this is the first study to integrate the association between the C282Y and H63D polymorphisms in the *HFE* gene and the risk of MS.

Materials and methods

PubMed, EMBASE and Web of Science were searched independently by two investigators to identify all relevant studies published before January 2021 that addressed the association between *HFE* polymorphisms and MS. The key words used in the search were: 'hemochromatosis' OR 'HFE' OR 'C282Y' OR 'H63D', 'multiple sclerosis' OR 'MS', 'polymorphism'

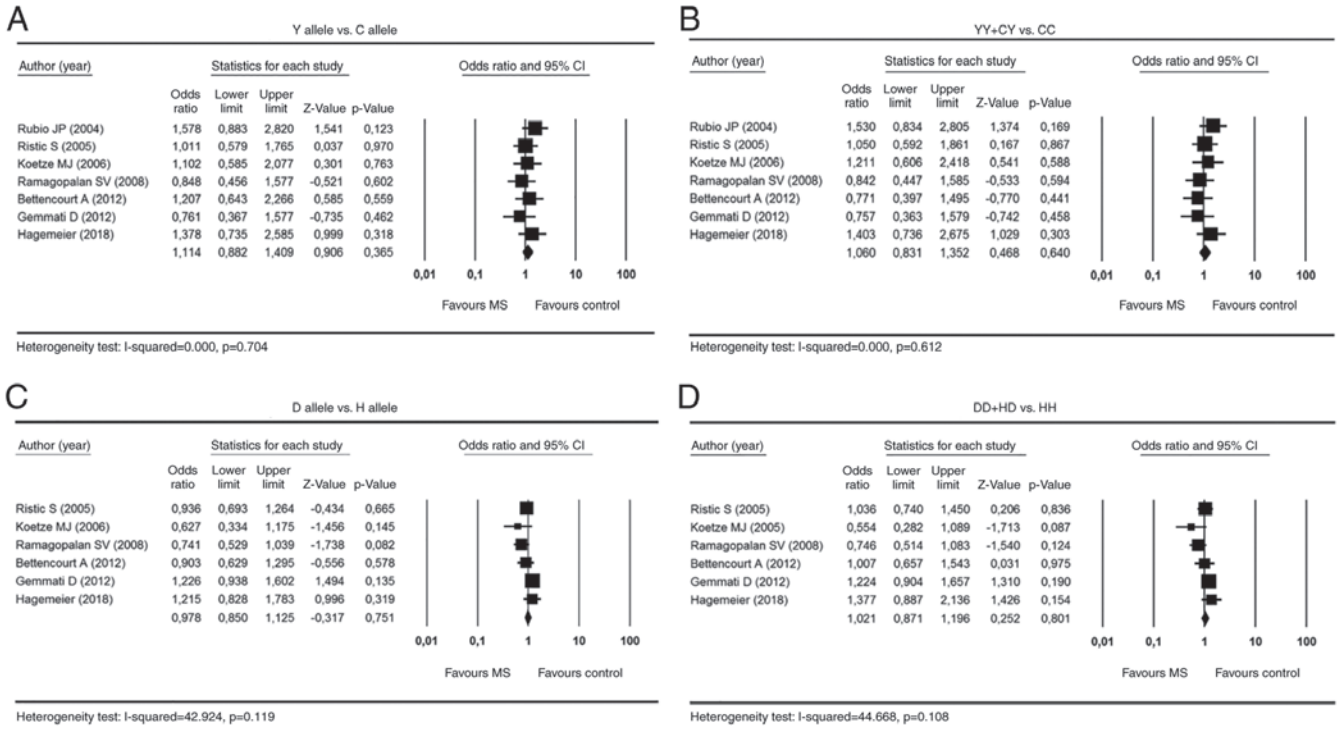

Figure 2. Forest plots of the associations between *HFE* polymorphisms and MS risk. (A) C282Y polymorphism and MS risk under the allele contrast model (Y vs. C). (B) C282Y polymorphism and MS risk under the dominant model (YY + CY vs. CC). (C) H63D polymorphism and MS risk under the allele contrast model (D vs. H). (D) H63D polymorphism and MS risk under the dominant model (DD + HD vs. HH). CI, confidence interval; MS, multiple sclerosis; *HFE*, hemochromatosis gene.

OR 'SNP' OR 'mutation' OR 'variant', where 'OR' was used as a Boolean modifier. The following information was collected from each study: First author, year of publication, country, ethnicity of study population, study design, number of cases and controls, and genotype and allele frequencies of the C282Y and H63D polymorphisms. A meta-analysis was performed in accordance with the PRISMA guidelines (28) using Comprehensive Meta-analysis 3.0 software (Biostatic Inc.).

The strength of the association between the C282Y and H63D polymorphisms and MS risk was estimated by odds ratios (ORs) with 95% confidence intervals (CIs). Due to the relatively small sample sizes of each study and the low frequency of variant alleles, as well as the practical clinical significance, a meta-analysis of only two comparison models was performed: The dominant model (YY + CY vs. CC or DD + HD vs. HH) and the allele contrast (Y vs. C or D vs. H). The distribution of genotypes in the control groups was tested for Hardy-Weinberg equilibrium using a χ^2 test.

A Cochran's Q statistic and I^2 tests were applied to quantify the heterogeneity between studies. Fixed/random effects models were used to calculate pooled ORs. Funnel plots and Egger's linear regression test were used to assess publication bias.

Results

A total of 7 studies that examined the association between *HFE* polymorphisms and MS were identified and included in the present meta-analysis. The final meta-analysis included 2,271 patients and 2,180 controls for the C282Y polymorphism (21-27), and 1,782 cases and 2,076 ontrols, for the H63D polymorphism (22-27). The flowchart of article selection and specific reasons for exclusion/inclusion are shown in Fig. 1. The characteristics of the studies and the *HFE* genotypes and allele distributions in MS patients and controls are provided in Table I. To include the data from the study by Ramagopalan *et al* (24) which lacked a control group, the previously reported C282Y and H63D genotype and allele frequencies from the Canadian population was used (29). All studies were performed in populations of Caucasian origin. The *HFE* genotype frequencies in the control groups of all studies were in Hardy-Weinberg equilibrium.

The results of the meta-analysis did not show a significant association between *HFE* polymorphisms and susceptibility to MS in any of the genetic comparison models (for Y vs. C: OR=1.11, 95% CI 0.88-1.41, P=0.365; for YY + CY vs. CC: OR=1.06, 95% CI 0.83-1.35, P=0.640; for D vs. H: OR=0.98, 95% CI 0.85-1.12, P=0.751; for DD + HD vs. HH: OR=1.02, 95% CI 0.87-1.20, P=0.801; Fig. 2). No heterogeneity was observed between studies in the meta-analysis (all P>0.05); therefore, the fixed effects model was applied.

No publication bias was found amongst the studies included in the meta-analysis. The shapes of the funnel plots for all tested models were symmetrical, and no statistical evidence of publication bias for any genetic model using Egger's linear regression test was found (P=0.656 for the Y allele model, P=0.371 for the dominant C282Y model, P=0.147 for the D allele model, and P=0.118 for the dominant H63D model).

Table I. Characteristics of studies included in the meta-analysis.

First author, year	Population studied	Study group, n	HFE C/Y genotypes, n (%)	HFE C/Y allele, %	HFE H/D genotypes, n (%)	HFE H/D allele, %	(Refs.)
Rubio *et al*, 2004	Australian (Tasmanian, Victorian)	MS, 489	CC, 395 (80.8); CY, 88 (18.0); YY, 6 (1.2)	C, 89.8; Y, 10.2	-	-	(21)
		Control, 104	CC, 90 (86.5); CY, 14 (13.5); YY, 0 (0.0)	C, 93.3; Y, 6.7	-	-	
Ristić *et al*, 2005	Croatian and Slovenian	MS, 314	CC, 291 (92.7); CY, 23 (7.3); YY, 0 (0.0)	C, 96.3; Y, 3.7	HH, 231 (73.6); HD, 80 (25.5); DD, 3 (0.9)	H, 86.3; D, 13.7	(22)
		Control, 400	CC, 372 (93.0); CY, 27 (6.8); YY, 1 (0.2)	C, 96.4; Y, 3.6	HH, 297 (74.3); HD, 90 (22.5); DD 13 (3.2)	H, 85.5; D, 14.5	
Kotze *et al*, 2006	Caucasian South African	MS, 118	CC, 95 (80.5); CY, 22 (18.6); YY, 1 (0.9)	C, 89.8; Y, 10.2	HH, 100 (84.7); HD, 17 (14.4); DD, 1 (0.9)	H, 91.9; D, 8.1	(23)
		Control, 102	CC, 85 (83.3); CY, 15 (14.7); YY, 2 (2.0)	C, 90.7; Y, 9.3	HH, 77 (75.5); HD, 25 (24.5); DD, 0 (0.0)	H, 87.7; D, 12.3	
Ramagopalan *et al*, 2008	Canadian	MS, 163	CC, 151 (92.6); CY, 12 (7.4); YY, 0 (0.0)	C, 96.3; Y, 3.7	HH, 119 (73.0); HD, 43 (26.4); DD, 1 (0.6)	H, 86.2; D, 13.8	(24)
		Control (C/Y, 881; H/D, 870)[a]	CC, 805 (91.4); CY, 76 (8.6); YY, 0 (0.0)	C, 95.7; Y, 4.3	HH, 578 (66.4); HD, 271 (31.1); DD, 21 (2.4)	H, 82.0; D, 18.0	
Bettencourt *et al*, 2011	Northern Portuguese	MS, 373	CC, 341 (91.4); CY, 31 (8.3); YY, 1 (0.3)	C, 95.6; Y, 4.4	HH, 251 (67.3); HD, 111 (29.8); DD, 11 (2.9)	H, 82.2; D, 17.8	(25)
		Control, 129	CC, 115 (89.1); CY, 13 (10.1); YY, 1 (0.8)	C, 94.2; Y, 5.8	HH, 87 (67.4); HD, 34 (26.4); DD, 8 (6.2)	H, 80.6; D, 19.4	
Gemmati *et al*, 2012	Northern Italian	MS, 414	CC, 401 (96.6); CY, 13 (3.1); YY, 0 (0.0)	C, 98.4; Y, 1.6	HH, 288 (69.6); HD, 113 (27.3); DD, 13 (3.1)	H, 83.2; D, 16.8	(26)
		Control, 414	CC, 397 (95.9); CY, 17 (4.1); YY, 0 (0.0)	C, 97.9; Y, 2.1	HH, 305 (73.7); HD, 101 (24.4); DD, 8 (1.9)	H, 85.9; D, 14.1	
Hagemeier *et al*, 2017	USA	MS, 400	CC, 353 (88.2); CY, 47 (11.8); YY, 0 (0.0)	C, 94.1; Y, 5.9	HH, 285 (71.2); HD, 104 (26.0); DD, 11 (2.8)	H, 84.2; D, 15.8	(27)
		Control, 150	CC, 137 (91.3); CY, 13 (8.7); YY, 0 (0.0)	C, 95.7; Y, 4.3	HH, 116 (77.3); HD, 28 (18.7); DD, 6 (4.0)	H, 86.7; D, 13.3	

[a]Control group consisted of 881 Canadian neonates for the C282Y mutation and 870 for the H63D mutation (29).

Discussion

The present meta-analysis showed no evidence of a significant association between the C282Y and H63D polymorphisms and the risk of MS. Conversely, these mutations did influence disease behavior rather than susceptibility, as some of the cited studies reported their influence on the onset or severity of MS. A higher MS disability score and disease progression have been shown to correlate with C282Y carriers (25,27) or H63D carriers (26). In our previous study, it was reported an earlier onset of disease in patients carrying the C282Y mutant allele (22). Recent research by Hagemeier *et al* (27) using quantitative susceptibility mapping MRI showed only a moderate association between iron-linked genetic polymorphisms and susceptibility to deep grey matter susceptibility. Furthermore, they found differences by sex in MS patients, suggesting that iron-related risk alleles are a potential risk factor for female MS patients. Gemmati *et al* (26) also reported high MS susceptibility associated with the H63 DD genotype in progressive female patients. These findings are consistent with the growing body of evidence showing that sex plays a significant role in the development, progression and treatment of MS. Moreover, our previous study in an animal model of MS showed that iron overload accelerates disease onset in female rats, but accelerates disease progression and increases mortality in male rats (13). However, due to the different study designs and insufficient original data in the studies included in the meta-analysis, analysis of the association between *HFE* polymorphisms and clinical features of MS, including age of onset and disease severity, could not be performed. As none of the studies provided sex-specific subgroup values for the *HFE* genotypes, it was not possible to perform a sex-based pooled analysis. In addition, mean serum iron, transferrin saturation and serum ferritin levels are known to be higher in individuals homozygous or compound heterozygous for the C282Y and H63D mutations compared with other *HFE* genotypes (16), but serum iron parameters were not available in MS patients, which should be investigated in the future.

Finally, it is well established that MS is a common complex disease whose susceptibility most likely results from the interplay of genes, environmental interactions and gene/environment interactions (30). Considering that ethnic confounding may be more problematic in disease susceptibility than in disease behavior, possible ethnic confounding effects were overcome in this meta-analysis as all studies included consisted of Caucasian populations.

In summary, no evidence was found showing that the C282Y and H63D polymorphisms contributed to MS susceptibility in the Caucasian population. The low frequency of the C282Y mutation and the compound C282Y/H63D genotype could possibly explain the lack of association in both the individual studies and the meta-analysis. Further studies with larger sample sizes addressing the role of *HFE* and other genetic variants related to iron regulation in the development and progression of MS are warranted.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

NSČ designed the study, performed the data analysis and wrote the manuscript. BĆC performed the data analysis and drafted the manuscript. VBL and BP interpreted the data, and drafted the manuscript. SR designed the study and drafted the manuscript. NSČ, BP and SR confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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