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Research article

The association between the C282Y and H63D polymorphisms of HFE gene and the risk of Parkinson's disease: A meta-analysis

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HIGHLIGHTS

- We performed a meta-analysis to assess the C282Y and H63D polymorphisms of HFE in PD.
- The C282Y polymorphism in HFE could be a potential protective factor for PD.
- No significant associations were found for any genetic model for the H63D mutation.

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ABSTRACT

Impaired brain iron homeostasis has been considered as an important mechanism in Parkinson's diseases (PD). There are indications that C282Y and H63D polymorphisms of HFE genes involved in iron metabolism might contribute to the pathogenesis of PD in some cases. However, the investigation of the relationship between PD and the two polymorphisms had produced contradictory results. We performed a meta-analysis to assess the C282Y and H63D polymorphisms of HFE in PD susceptibility. PubMed, EMBASE and Web of Science were systematically searched to identify relevant researches. The strict selection criteria and exclusion standard were applied. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of associations. A fixed-effect or random-effect model was selected, depending on the results of the heterogeneity test. Fifteen studies were included in the meta-analysis (eight studies with 1631 cases and 4548 controls for C282Y; seven studies with 1192 cases and 4065 controls for H63D). For the C282Y polymorphism, significant associations were observed in the Recessive model (YY vs CY + CC: OR = 0.22, 95% CI = 0.09–0.57, $P = 0.002$). This indicated that the C282Y polymorphism in HFE might be a potential protective factor for PD. However, no significant associations were found for any genetic model for the H63D polymorphism, suggesting that the H63D polymorphism might not be associated with PD.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease, characterized by the loss of pigmented dopaminergic neurons in the substantia nigra pars compacta (SNc). Although the exact mechanisms underlying the etiology of PD are not clear, increasing evidence has shown that nigral iron accumulation contributed to the neurodegeneration of dopamine neurons in PD [1–5]. Iron-induced oxidative stress via Fenton reaction is believed to be the main putative mechanism underlying iron-induced neurodegeneration of dopamine neurons.

Due to the important role of iron accumulation in PD, elevation of total body iron stores or iron overload might be one of the risks of PD. Our previous studies have shown that misregulation of iron transporters including divalent metal transporter 1 and ferroportin 1 were involved in the nigral iron accumulation [6–8]. Hereditary hemochromatosis (HH) is an autosomal recessive disorder of iron metabolism, leading to increased iron absorption and excessive iron accumulation [9]. It is reported that HH is most often caused by mutations of HFE gene on chromosome 6p21.3. Two mutations of this gene (C282Y and H63D) have been described to contribute to iron overload. Evidence has showed that these two polymorphisms in the HFE gene could trigger serum iron overload. In addition, HFE protein has been reported to be involved in the regulation

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of iron homeostasis by binding to the transferrin receptor (TfR) and decreasing the transport of iron [10]. Studies have also demonstrated that an interaction between HFE and TfR was lost when HFE is mutated [10], suggesting that HFE might play a key role in regulating iron transportation to cells. This leads to the hypothesis that HFE gene mutations might be a possible mechanism contributing to iron overload and the pathogenesis of PD. However, studies on correlation between the HFE mutations and risk of PD have produced conflicting results [11–16]. Some reports indicated that there was a positive association between HFE mutations and risk of PD, and others showed no association was observed. Thus, in the present study, we performed a meta-analysis to clarify the association between HFE gene polymorphisms and risk of PD.

2. Methods and materials

2.1. Data collection

Two investigators independently reported studies on the associations between HFE polymorphisms and PD. The PubMed, EMBASE and Web of Science, from their inception to November 25, 2014, were searched to identify potentially relevant researches. The following search strategy was used, which combined both the medical subject heading (MeSH) and keywords (("HFE" or "C282Y" or "H63D" or "Cys282Tyr" or "His63Asp" or "rs1800562" or "rs1799945") and ("Parkinson disease" or "Parkinsonism" or "Parkinson's disease" or "Parkinson" or "PD") and ("SNP" or "SNPs" or "single nucleotide polymorphism" or "polymorphism" or "genetic polymorphism" or "mutation" or "variant" or "variation")). When necessary, the authors of articles were contacted to obtain missing data. The search was done without restriction on language, but only published articles in English were included in the last.

2.2. Selection criteria

Two investigators independently identified potentially relevant studies and evaluated each trial according to predefined eligibility criteria. Studies were included if they matched the following criteria: (1) association study, using a cohort-design or case-control; (2) available data for C282Y or H63D mutations with risk of PD; and (3) the genotypes distribution in the control population were in Hardy–Weinberg equilibrium (HWE). The exclusion criteria were (1) reviews and animal studies; (2) lack of data on genotype number or frequency; and (3) genotype distribution in the control groups was not consistent with HWE. If the same author published more than one study, only the most recent or complete report was included in the meta-analysis.

2.3. Data extraction

After removing duplicate studies and adding any additional studies, two investigators extracted data independently in a standard time and entered the information into a common database. When discrepancies arose, all investigators assessed the data. The following information was collected: first author, year of publication, country, ethnicity, characteristics, study design, sample sizes of patients and controls, genotype numbers, and *P* value for HWE. Therefore, we combined the data and analyzed the pooled controls from those series as one group and compared with another one from the cases.

2.4. Statistical analysis

We performed our meta-analysis based on the PRISMA checklists and followed the guideline [17]. Hardy–Weinberg equilibrium (HWE) was evaluated for each study by chi-square test in control groups, and $P<0.05$ was considered a significant departure from HWE. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the strength of the association between C282Y/H63D SNPs and susceptibility to PD. Pooled ORs were per-

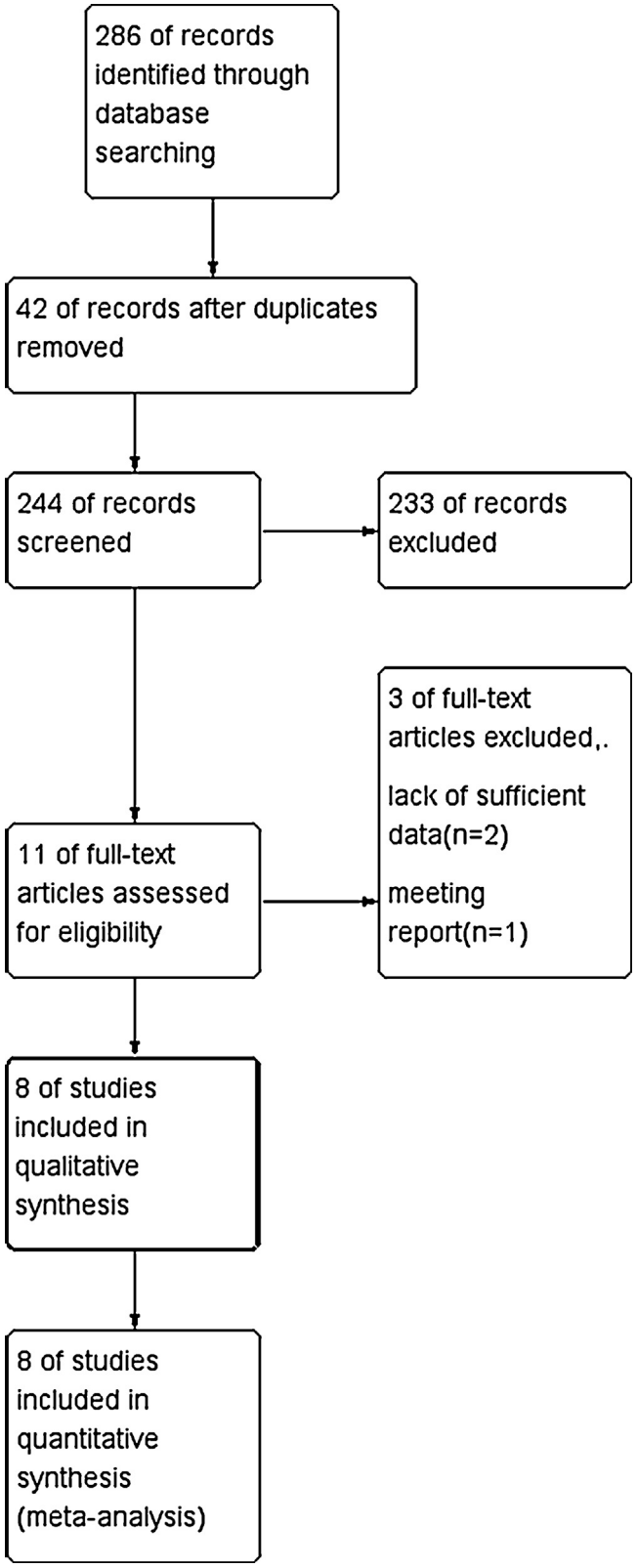

Fig. 1. Flow chart of study selection.