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Association between the prothrombin G20210A mutation and sudden sensorineural hearing loss in European population: A meta-analysis

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ABSTRACT

Purpose: Epidemiological studies have reported inconsistent findings on the association between the prothrombin G20210A mutation and sudden sensorineural hearing loss (SSNHL) in European population. The aim of this meta-analysis was to clarify the association of this polymorphism with SSNHL in European population.
Methods: PubMed, Embase, and the China National Knowledge Infrastructure (CNKI) were searched up to August 1, 2014. We used STATA12.0 to calculate summary odds ratios (ORs) with 95% confidence intervals (CIs).
Results: Eight studies including 1972 patients were identified. Pooled data showed no significant association between the prothrombin G20210A mutation and risk of SSNHL in European population : A vs. G (OR = 1.645, 95% CI:0.78-3.49,POR = 0.194); AG vs.GG (OR = 1.660, 95% CI:0.77-3.60,POR = 0.199).
Conclusions: The present meta-analysis suggests that the prothrombin G20210A mutation is not significantly associated with an increased risk of SSNHL in European population.

Introduction

Sudden sensorineural hearing loss (SSNHL) is defined as hearing loss of 30 dB or more over at least three contiguous frequencies occurring within three days or less [1]. SSNHL is a frequent disease in otorhinolaryngology and the estimated annual incidence is 20 per 100,000 persons [2]. The pathogenesis of SSNHL emains unknown despite being recognized since 1944 [3]. Various theories have been developed about the pathogenesis, including the autoimmune theory [4], the vascular theory [5,6], the infectious theory [7], and the theory of rupture of the membranes to the inner ear or within the inner ear [8].

To gain insight into mechanisms of vascular thrombosis of the inner ear, many studies investigated patients with sudden sensorineural hearing loss of the pancochlear type and sudden deafness for the presence of inherited prothrombotic risk factors in the past few years. Among the inherited prothrombotic risk factors that have been characterized is a single nucleotide change –G to A– at position 20210 in the sequence of the 3'-untranslated region of the human prothrombin gene encoding coagulation factor II (FII) [9].It was found to be a major cause of thromboembolic disease and thus involved in many diseases, such as Retinal vein occlusion [10],recurrent pregnancy loss [11], and Acute myocardial infarction [12]. However, it remains unknown whether the prothrombin G20210A mutation is associated with SSNHL in isolation. Epidemiological studies on the association between the prothrombin G20210A mutation and SSNHL in European population conveyed inconsistent results [13–20]. The discrepancies in the above findings may be due to a single study with low statistical power, various sample size, different inclusion and exclusion criteria and uncorrected multiple hypothesis testing. Therefore,this meta-analysis was designed to summarize the evidence on the association between the prothrombin G20210A mutation and SSNHL in European population.

Materials and Methods

Search Strategy and Selection Criteria

A comprehensive electronic search of PubMed, Embase, and the China National Knowledge Infrastructure (CNKI) were conducted. The following key words or combination of terms were used: "prothrombin" and "genetic polymorphism" or "mutation" and "sudden sensorineural hearing loss" or "SSNHL". The latest search was run on August 1, 2014, without any language, country, or publication status restrictions. We only selected published manuscripts (including their online supporting materials). All eligible studies were independently retrieved by two authors (Shu and He). Study were included if they met the following criteria:(1) evaluation of the MTHFR gene polymorphism and SSNHL risk; (2) case–control or cohort studies; (3) with sufficient data to infer the results. (4)all participants were European. While the major reasons for exclusion of studies were as follows: (1) insufficient or error data; (2) lack of control-group or genotype distribution is deviation from the test of Hardy–Weinberg equilibrium (HWE) in controls.

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When multiple publications reported on the same or overlapping data, we used the most recent or largest population as recommended by Little et al. [21].

Data Extraction and Quality Assessment

The following data were extracted from the studies: the first author's surname, year of publication, the country where the study was performed, geographic location, total number of cases and controls, deviation from Hardy-Weinberg equilibrium (HWE) in controls, source of controls (hospital-based or population-based), genotyping method, distribution of alleles and genotypes in case and control groups. When studies did not include the required information, we contacted the authors to obtain the relevant data. Two reviewers (Shu and He) independently extracted data and reached consensus on all of the items. Any discrepancies we resolved by discussion. A third party was involved when necessary.

Statistical Analysis

The association of the prothrombin G20210A mutation with the SSNHL susceptibility was estimated by calculating odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) under all genetic models. Data analysis was performed using STATA Software (version 12.0, Stata Corp.). $P < 0.05$ was considered statistically significant. Two comparison models for the prothrombin G20210A mutation were evaluated: an allele model (A vs. G)and a co-dominant model (AG vs. GG).

The between-study heterogeneity was examined by Q statistic test. P value <0.1 was considered statistically significant [22]. When P value > 0.10 and I2 < 50%, the between-study heterogeneity was not significant, we used the fixed-effects (Mantel–Haenszel) model, otherwise, the random-effects (DerSimonian–Laird) model was used to calculate the data.

Sensitivity analysis was performed by sequentially removing an individual study each time to check whether any single study could bias the overall estimate [23]. The potential publication bias was investigated using Begg' funnel plot and Egger's regression test [24]. $P < 0.05$ was regarded as statistically significant. In our meta-analysis, the P value for the control population in HWE was calculated by a Chi-square test again. The HWE was considered statistically significant, when the P value was less than 0.05 [25].

Results

Study Characteristics

Eight studies that met the inclusion criteria were included in the meta-analysis [13–20]. The detailed selection process is illustrated in Fig. 1. The characteristics of the extracted information from each article are summarized in Table 1. Among the eligible studies, a total of 1972 subjects (693 SSNHL cases, 1279 healthy pregnancy controls) were included for this meta-analysis. All the genotype frequencies in the control populations were in agreement with HWE.

Quantitative Synthesis of Data

The relationship between the prothrombin G20210A mutation and the risk of SSNHL was explored through eight case–control studies including 1972 subjects(693 cases, 1279 controls). No significant association was observed under all genetic models [allele model: A vs. G, OR = 1.645, 95% CI:0.78-3.49,POR = 0.194; co-dominant model: AG vs. GG, (OR = 1.660, 95% CI:0.77-3.60,POR = 0.199] (Fig. 2). The results are displayed in Table 2.

Sensitivity Analysis

Sensitivity analysis, after removing one study at a time, was performed to evaluate the stability of the results. For the prothrombin G20210A mutation, when successively excluded one study(data

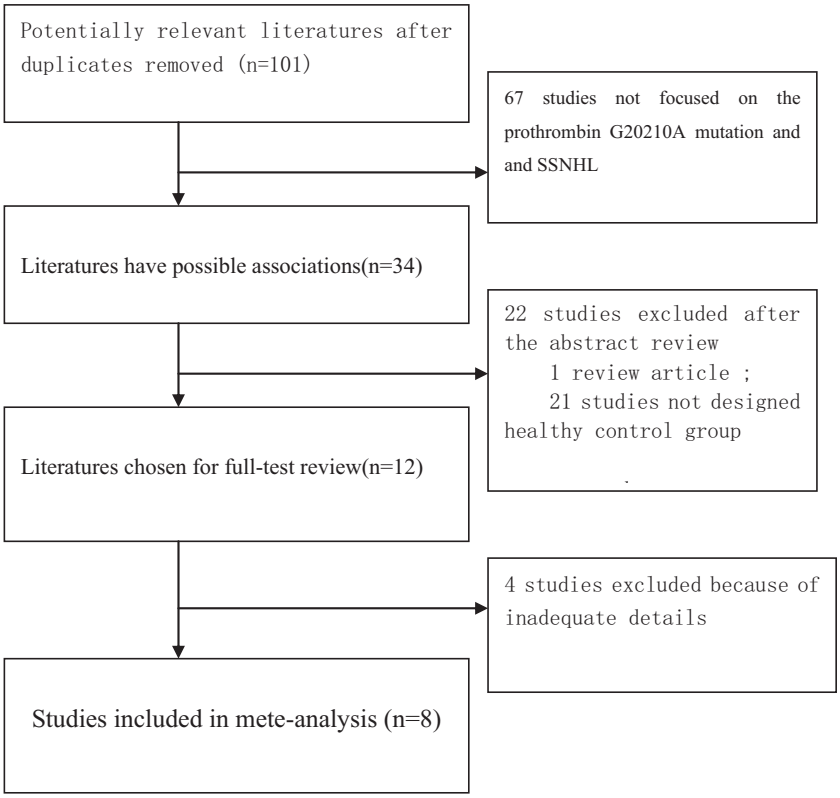

Fig. 1. Flow chart of the study selection process.