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Review article

Genetic factors of cervical spondylotic myelopathy-a systemic review

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ABSTRACT

Background: Cervical spondylotic myelopathy (CSM) is a degenerative disorder of the neck. Recent studies have reported the roles of single nucleotide polymorphisms and abnormal gene expression in the etiology and development of CSM. However, a systemic review of these findings is currently unavailable.
Methods: A systemic review of genetic factors of CSM was conducted through searching PubMed and EMbase databases. A total of 9 studies were included in this study, which included 8 genes: brain derived neurotrophic factor (BDNF), osteopontin (OPN), bone morphogenic protein (BMP) 4, collagen IX, vitamin D receptor (VDR), apolipoprotein E (ApoE), hypoxia-inducible factor α (HIF-1α), and cyclooxygenase 2 (COX-2).
Results: The polymorphisms of 6 genes (OPN, BMP-4, collagen IX, VDR, HIF-1α) showed significant association with the susceptibility to or risk of CSM. The polymorphisms of 3 genes (BMP-4, ApoE4, HIF-1α) were significantly associated with the postoperative outcome. The polymorphism of BDNF, VDR, and expression of COX-2 were associated with the severity of disease.
Conclusion: This review demonstrates that 8 genes were associated with CSM although there is no repeated study. This review also suggests that large scale and high quality studies are needed to provide more reliable evidence for future evaluation.

1. Introduction

Cervical spondylosis with myelopathy or cervical spondylotic myelopathy (CSM) is the most common disorder that causes spinal cord dysfunction in the elderly population. Although the accurate incidence and prevalence of CSM are currently unavailable, a study in eastern Asia reported that the incidence of CSM-related hospitalizations was 4.04 per 100,000 person-years [1]. Although the onset of CSM can occur in young adults, most studies observed higher incidences in older and male patients [2]. Thus, CSM can be considered a common disorder in the elderly. Surgical decompression is a well-established treatment method to halt the progression of the disease and relieve the preoperative symptoms for moderate to severe symptomatic CSM, but is not always effective [3].

CSM is a disease caused by the degeneration of the spinal structures, which leads to narrowing or compression of the spinal canal and subsequent spinal cord dysfunction and progressive disability [4]. The degeneration of spinal structures is noninflammatory and often accompanied by facet joint osteoarthritis, as well as pathologic changes in the posterior longitudinal ligament (PLL) and ligamentum, such as hypertrophy and ossification [5]. Also, a postmortem study of CSM patients identified spinal cord ischemia, such as spinal cord necrosis and gray matter cavitations [6]. The observation of elevated BDNF, NT-3, trkB and trkC expression in motoneuron areas in a CSM animal model further supports the involvement of spinal cord pathological changes in CSM [7]. Glutamatergic excitotoxicity, free radical generation, lipid peroxidation, inflammation, and ischemia were postulated to play a role in the pathology of CSM [2].

The etiology and mechanism of progression of CSM are currently unclear. Some environmental factors, including age, gender, smoking, obesity, and trauma were reported to be associated with CSM [8]. A genetic factor is also thought to be associated with the degeneration of CSM [9]. However, the detailed cellular and molecular mechanisms of CSM remain to be elucidated. Recent studies have reported the role of single nucleotide polymorphisms in genes and abnormal gene expression in the etiology and

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development of CSM [8,10–17]. A review study summarized single nucleotide polymorphisms of the collagen gene in ossification of the posterior longitudinal ligament (OPLL) cases [18], and a review summarized the associations between MMP-2, collagen IX and degenerative disc disease, and collagen VI/XI and ossification of the OPLL [19]. A recent narrative review summarized the association of VDR ApaI and TaqI polymorphism, the tryptophan allele of the collagen 9A2 gene, and the ApoE4 allele with the severity, development, and outcomes of CSM [20]. However, it still lack a systematic review that updates all of the findings on the involved genes in CSM.

Exploration of the molecular mechanisms of this intractable disease will lead to the development of reparative and regenerative treatments for human CSM. The aim of this study was to review the current findings in the molecular mechanism of CSM and systematically analyze studies that tested the role of a gene in the etiology, development, and prognosis of CSM.

2. Methods

2.1. Identification of relevant studies

Electronic searching of PubMed and EMbase databases was performed in April 2017 using the keywords: "cervical spondylotic myelopathy" plus "genetics", "gene", "polymorphism", "molecular", or "inherited". Then, the abstracts were reviewed one-by-one. We excluded reviews or comments and research articles that were not written in English, not for humans, and no gene was being identified. We only included studies where a specific gene was accurately identified in human (Fig. 1).

2.2. Eligibility criteria

A systematic review of original studies of gene expression or genetic polymorphisms in patients with CSM was conducted. Reports on gene expression or polymorphisms measured in peripheral blood or disc tissues were eligible for review. A study was included in the analysis when: 1) CSM was accurately diagnosed, 2) A specific gene was identified, 3) association with susceptibility and/or clinical outcome was analyzed, and 4) it is an original study. Studies were excluded if: 1) A study was conducted in animals or *in vitro*; or 2) review or studies not written in English.

2.3. Data extraction

The abstract of each study was screened and the full-text articles of potentially relevant studies were then assessed. Data were extracted from the retrieved papers. Disagreements were resolved by discussion in a meeting that included experts from the Department. The study selection process was presented in a flow diagram (Fig. 1). From each full-text article, we extracted data on experimental design, the number of cases in each group, demographic characteristics of patients and control individuals, gene expression or polymorphism, tissue type, and the results. Risk of bias was assessed by evaluating choice of study design, selection of study population, allocation of control individuals, and quality of assay used.

3. Results

The literature search identified 37 articles from PubMed and EMbase using the key words: "cervical spondylotic myelopathy" and "polymorphism", or "genetics", or "gene", or "inherited". Among them, 33 articles were identified by cervical spondylotic myelopathy and genetics, 14 articles were identified by cervical spondylotic myelopathy and gene, 9 articles were identified by cervical spondylotic myelopathy and gene polymorphism, and 3 articles were identified by cervical spondylotic myelopathy and inheritability (inherited). After excluding 4 articles not written in English, 6 reviews or comments, 8 studies at cell level or animal studies, one that was not CSM, and 8 articles without a gene being identified, 9 articles were finally included in the analysis (Fig. 1).

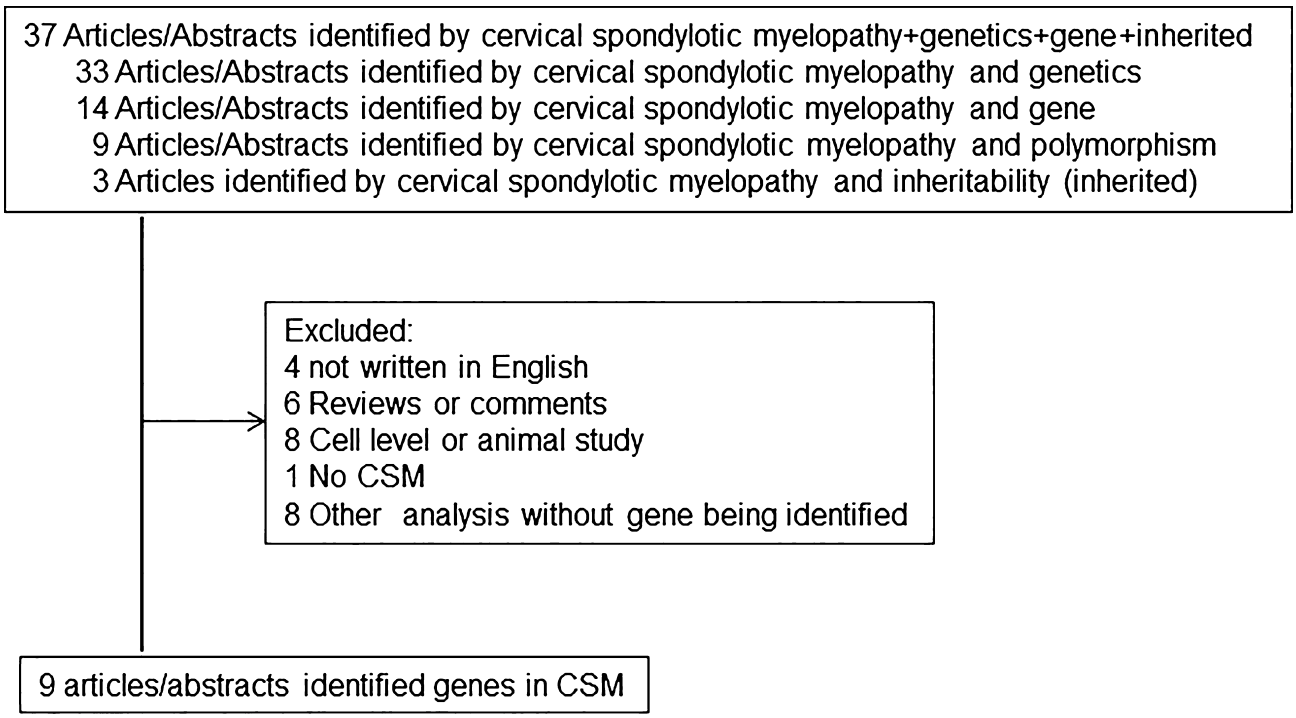

Fig. 1. A flowchart of literature search strategy. A flowchart of the included and excluded studies in the current analysis.