Genetic Odyssey to Ossification of the Posterior Longitudinal Ligament in the Cervical Spine: A Systematic Review

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Despite numerous studies, the pathogenesis of ossification of the posterior longitudinal ligament (OPLL) is still unclear. Previous genetic studies proposed variations in genes related to bone and collagen as a cause of OPLL. It is unclear whether the upregulations of those genes are the cause of OPLL or an intermediate result of endochondral ossification process. Causal variations may be in the inflammation-related genes supported by clinical and updated genomic studies. OPLL demonstrates features of genetic diseases but can also be induced by mechanical stress by itself. OPLL may be a combination of various diseases that share ossification as a common pathway and can be divided into genetic and idiopathic. The phenotype of OPLL can be divided into continuous (including mixed) and segmental (including localized) based on the histopathology, prognosis, and appearance. Continuous OPLL shows substantial overexpression of osteoblast-specific genes, frequent upper cervical involvement, common progression, and need for surgery, whereas segmental OPLL shows moderate-to-high expression of these genes and is often clinically silent. Genetic OPLL seems to share clinical features with the continuous type, while idiopathic OPLL shares features with the segmental type. Further genomic studies are needed to elucidate the relationship between genetic OPLL and phenotype of OPLL.

Keywords: Ossification of posterior longitudinal ligament, Myelopathy, Genomics, NLRP1, BMP, SSH2

INTRODUCTION

Ossification of the posterior longitudinal ligament (OPLL; MIM 602475) is a hyperostotic condition that results in ectopic calcification of the posterior longitudinal ligament (PLL) and leads to a reduced range of motion and potential spinal cord compromise.1,2 OPLL was first reported by Key in 1838 and described in detail by Tsukimoto in 1960.3,4 Two centuries have passed since the discovery of this disease, and nearly a century has passed since the specific form of the disease was confirmed, but we still do not know the exact cause, pathogenesis, and treatment of OPLL.1–8 Numerous studies over the last several decades have suggested the involvement of multiple etiologic factors in the development of OPLL, including genetic factors, mechanical stress, nutrition, and secondary changes caused by systemic disease.9

With regard to the pathogenesis of OPLL, on one hand, OPLL demonstrates racial differences in its incidence, which is especially high in East Asian males.10,11 A previous study in North America showed that the prevalence of OPLL varied among races: 4.8% in Asian Americans, 1.3% in Caucasian Americans, 1.9% in Hispanic Americans, and 3.2% in Native Americans.12
The prevalence of OPLL was found to be 26% in the parents and 29% in the siblings of probands from 347 OPLL families, which is significantly higher than that in the general population.13 This finding implies that OPLL is a genetic disease. On the other hand, the nongenetic factors associated with OPLL include age, diabetes mellitus, obesity, exercise, and mechanical stress. The majority of OPLL cases occur after age 50, which means that OPLL is related to degenerative disease. Previous studies also reported that OPLL was associated with a vitamin A-rich diet, plasma pentosidine levels, and femoral neck bone mineral density.12,14,15

Many investigators have performed case-control association studies, affected sibling-pair linkage studies, and candidate gene association studies, and they identified many genes or loci that are linked to OPLL susceptibility. However, replication studies have failed to verify these results, even in the same ancestry groups as the original studies.16 Next-generation sequencing (NGS) has recently emerged, and the genetic odyssey of OPLL has moved to a new direction. The purpose of this study was to review systematically and summarize genetic and genomic studies on OPLL of the cervical spine, and to make a suggestion which will help us to guide our future OPLL studies.

MATERIALS AND METHODS

A comprehensive literature search was performed using PubMed, Embase, and the Cochrane Library for all journal articles published from January 2000 through October 2021. We also manually searched reference lists. Key words used in the search included “ossification of the posterior longitudinal ligament,” “genetics,” and “genomics.” The terms were searched individually or in combination. Appropriate articles for our review were selected based on scientific investigations on the genetic inheritance and susceptibility patterns of OPLL in humans. The search results were screened by title and abstract for the following exclusion criteria: duplicate studies; case reports, letters, comments, reviews, or technical notes; animal studies; and OPLL in the thoracic spine. After eliminating the excluded papers, full-text articles were obtained, and studies were thoroughly screened again using the same exclusion criteria. We excluded the following articles: combined diseases such as diffuse idiopathic skeletal hyperostosis (DISH) and ankylosing spondylitis (AS); redundant papers; and those without any description of mean values, the standard deviation, or the number of patients in each group. We limited our results to articles in the English language. In the case of overlapping study populations, we excluded patients described twice or used the most recent publication.

RESULTS

1. Systematic Search and Identification of Relevant Papers
An initial literature search using the chosen subject headings identified 129 studies in PubMed, 138 studies in Embase, and 2 studies in the Cochrane Central Register of Controlled Trials. Among these 269 studies, 71 were duplicates and were thus excluded. After screening titles and abstracts, 86 of the 198 remaining papers were excluded from our analysis because they were case reports, review articles, letters, technical notes, or animal experiments. Ten papers written in Japanese or Chinese were excluded, and 6 studies that dealt with OPLL in the thoracic and lumbar spine were excluded. The remaining 96 studies were subjected to a full-text review, and another 35 were excluded. These 26 articles were excluded because the studies used a mixed group including patients with other rheumatic diseases such as AS (n = 21), no description of the standard deviation (n = 8), and indirect comparative studies or single group studies (n = 6). Finally, this systematic search found 39 gene-expression screening studies using real-time quantitative polymerase chain reaction, 6 genome-wide association studies (GWAS), 2 NGS studies, 7 proteomic tissue expression analyses, and 7 micro-RNA expression analyses. A detailed process is shown in Fig. 1.

2. Pathogenesis I: Review of Studies That Conducted Screening of a Few Genes
Many research groups have proposed that genes related to bone, collagen, and inflammation might be associated with the initiation and progression of OPLL by using several methods such as genetic linkage analysis, positional cloning, and association studies.17 The expression levels of the osteoblast-specific genes encoding alkaline phosphatase (ALP), osteocalcin (OCN), and type I collagen (COL I), were upregulated in OPLL patients, as shown in Table 1.18-23 However, it remains unclear whether upregulated expression of bone and collagen-related genes is the cause of this disease or an intermediate result of the ossification process.24 In addition, some ossification-related genes such as BMP, RUNX2, and TGFβ families were introduced as causal genes in the development of OPLL based on genotyping.21,24-26 The logic of these studies is that some suspected genetic variations that researchers assumed to be causal variations showed statistically significant differences in case-control studies. This may be valid if only a few variations demonstrate sta-
tistically significant differences between the 2 groups. However, there were thousands of variations show statistically significant differences in case-control studies. Even if, those variations were closely related with the OPLL, it is unknown whether they were causal variation or intermediate results.

3. Pathogenesis II: Review of Genomic Variation Discovery Studies

Genomic variation detection can be divided into discovery and screening.27 Discovery involves the identification of variations that are not yet known, while screening pertains to known variations.27 Causative genetic variations of OPLL have not been clearly elucidated, and genomic studies must discover all genes, excluding the researcher’s prejudice. Nakajima et al.16 performed the first GWAS study that discovered variant loci in the whole genome, and they identified 6 susceptibility loci for OPLL. Their subsequent study suggested that RSPO2 might be a susceptibility gene for OPLL based on genetic and functional data.28 However, the RSPO2 gene did not show a significant difference in other researchers’ studies, including a whole-exome sequencing (WES) study.29

Two WES studies that used the most up-to-date and precise methods to discover causal variations were published by researchers from Korea and China.29,30 One paper included 28 patients with OPLL (67%, continuous/mixed type) and suggested that variants of the PTC1 and COL17A1 genes might contribute

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### Table 1. Differential expression ratio of OPLL for the various osteogenic marker gene

| Study              | No. of OPLL | No. of controls | ALP DE | ALP p-value | OCN DE | OCN p-value | COL I DE | COL I p-value |
|--------------------|-------------|-----------------|--------|-------------|--------|-------------|----------|---------------|
| Yamamoto et al.21  | 5           | 5               | 1.55   | <0.05       | N/D    | N/D         | N/D      | N/D           |
| Tsukahara et al.12 | 3           | 3               | 1.76   | SD, 0.04    | 2.83   | 0.08        | 1.66     | 0.16          |
| Yang et al.19,20   | 20          | 18              | 1.79   | <0.01       | 1.72   | <0.01       | 1.62     | <0.01         |
| Tanaka et al.13    | 18          | 14              | 1.8    | N/D         | 2.71   | <0.001      | 3.31     | <0.001        |
| Yang et al.18      | 21          | 16              | 2.71   | <0.001      | 2.71   | <0.001      | 3.31     | <0.001        |

OPLL, ossification of the posterior longitudinal ligament; ALP, alkaline phosphatase; OCN, osteocalcin; COL I, type I collagen; DE, differential expression; SD, standard deviation; N/D, no description.
to the development of OPLL. Changes in these markers, such as ALP, BMP2, and osteopontin, have been observed in OPLL fibroblasts in vitro, suggesting that they may play a role in the development or progression of the disease.

4. Pathogenesis III: Role of Mechanical Stress in the Development/Progression of OPLL

Mechanical stress could induce osteogenic differentiation of PLL fibroblasts in vitro, which is expressed as the upregulation of osteogenic markers, including OCN, ALP, and COL I. Other researchers have reported that numerous genes showed upregulated expression levels in response to mechanical stress, such as ALP, BMP2, and osteopontin, indicating that mechanical stress may be a causal factor of OPLL.

5. Two Distinct Phenotypes of OPLL

One reason for the uncertain pathogenesis is that OPLL is a disease named based on a radiological finding regardless of cause and pathogenesis. According to the definition of the disease name, all patients showing any ossification or calcification at the PLL can be diagnosed with OPLL. The disease needs to be classified based on its cause and pathogenesis because ectopic osteogenesis (ossification and calcification) is frequently found even in healthy people in various organs and tissues, including connective tissues, blood vessels, and skeletal muscle. In addition, some systemic diseases such as hypoparathyroidism, DISH, AS, and potentially schizophrenia sometimes induce paravertebral ligamentous ossification.

Therefore, clinically insignificant calcifications or ossification of PLL may be better excluded from the diagnosis of OPLL. It is well known that OPLL can be classified into 4 types based on the shape of the ossified region using plain radiographs of the cervical spine in the lateral view: continuous, segmental, mixed, and localized. However, researchers suggested that it would be better to divide OPLL into only 2 types (continuous and segmental) based on the histopathology, prognosis, and appearance. The mixed type of OPLL is regarded as a subcategory in which segmental ossification is added to the continuous
type of OPLL. The localized type of OPLL is referred to as the circumscribed or unclassified type of OPLL, and is regarded as a kind of the segmental type of OPLL. Differential points between continuous/mixed and segmental/localized OPLL are described in Table 2.

A previous study demonstrated that ALP activity in continuous OPLL, segmental OPLL, and non-OPLL was 2.56 ± 0.05, 1.21 ± 0.11, and 1.00 ± 0.05, respectively. Other researchers also reported that the expression level of ALP, OCN, and COL I showed significant step-wide decrease, which was found most prominently in continuous OPLL, followed in order by segmental OPLL and non-OPLL. The researchers stated that spinal ligament cells derived from continuous OPLL tended to be more easily mineralized than those from segmental OPLL patients. From a clinical point of view, continuous OPLL requires careful observation of cervical myelopathy, whereas segmental OPLL is often clinically silent. A previous meta-analysis demonstrated that the continuous/mixed type accounted for 77% of the patients who underwent surgery due to cervical myelopathy with OPLL. The progression rate of ossification was reported to be 75% in patients with continuous OPLL and 38% in those with segmental OPLL. Another study showed 72% of patients with continuous/mixed OPLL had involvement in the upper cervical region such as C2. It may be necessary to distinguish clinically significant continuous OPLL from the asymptomatic segmental type based on genetic, biochemical, and clinical differences.

6. Suggestion for the Development of OPLL

We may summarize 2 mechanisms and 2 types of OPLL, as shown in Fig. 2. One is named idiopathic OPLL, which may be triggered by mechanical stress, comorbid diseases, and specific nutritional patterns. Mechanical stress to the cervical spine is usually focused on low cervical spine, high mobile segments. Segmental OPLL usually occur at the segments, but continuous OPLL usually involve upper cervical spine. Segmental or localized OPLL may be developed by this mechanism. This type

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Table 2. Two different phenotypes of cervical OPLL

| Item                        | Continuous/mixed | Segmental/localized |
|-----------------------------|------------------|---------------------|
| Upper cervical (C2, 3) involve | Frequent         | Rare                |
| Lower cervical (C5/6/7) involve | Sometimes       | Frequent            |
| Mean age                    | Younger          | Older               |
| Progression rate            | Fast             | Slow                |
| Need for surgical treatment | Sometimes        | Rare                |

OPLL, ossification of the posterior longitudinal ligament.

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Fig. 2. Hypothetic pathogenesis of ossification of the posterior longitudinal ligament (OPLL). The phenotype of OPLL is divided into continuous (including mixed) and segmental (including localized). The continuous type of OPLL demonstrates much higher expression of endochondral ossification genes encoding osteocalcin (OCN), alkaline phosphatase (ALP), and type I collagen (COL I) than the segmental type of OPLL. Genetic OPLL showed involvement of less stressed cervical region such as C2 and frequent surgical treatment, which is similar with continuous type of OPLL. DM, diabetes mellitus; Vit-A, vitamin A.
may show moderate over expression of ALP, OCN, and COL I. Rapid increase of surgery for OPLL over the past 10 years may mean that OPLL can be developed regardless of genetic vulnerability because it is difficult to triple the number of genetic diseases for 10 years. The other is named genetic OPLL, which occurs in patients with variations in inflammatory genes such as NLRP1 and SSH2. Levels of inflammatory biomarkers such as CRP were found to remain high in OPLL patients and were positively associated with OPLL progression. Genetic OPLL may even show involvement in the upper cervical regions with less mechanical stress. In an epidemiologic study from US, Asian American underwent 53% more spine surgeries than the US overall. This may mean that genetic OPLL often seems to induce cervical myelopathy and more often requires surgical treatment than the idiopathic OPLL and genetic OPLL needs to surgical treatments more than idiopathic OPLL. These features of genetic OPLL are observed in continuous OPLL. Although the genetic differences among types of ossification remain to be elucidated, genetic and genomic studies may provide new etiologic insights into how the type of OPLL relates to the causal genetic variation and the prognosis.

7. Limitations
There are some limitations that need to be acknowledged and addressed regarding the present study. The first limitation concerns a narrative review. We tried to search all genetic and genomic studies and offer clear evidence. We performed a systematic search and found 60 papers. Most of searched studies suggested misleading candidate genes that studied with single or a few genes and variants addressed one at a time by single team with small sample size. The authors tried to summary all reported results without bias because following the systematic review protocol could rather lose objectivity. The second, there are few evidence that genetic OPLL make continuous type ossification. It is entirely our hypothesis. Although genetic OPLL showed similar feature with continuous type of OPLL, there are many things that are difficult to explain by the reason. Further studies are necessary to find out the difference in genetic variations by type of OPLL.

CONCLUSION
OPLL may develop from genetic vulnerabilities and idiopathic factors, including mechanical stress. It is not clear whether OPLL is a complex genetic disease or a combination of various diseases that share a process of calcification/ossification as a common pathway. Genetic OPLL seems to share clinical features with the continuous type, while idiopathic OPLL shares them with the segmental type. Further genomic studies with clear phenotypic classifications may provide further insights into the disease.

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