Ossification of the posterior longitudinal ligament refers to pathological mineralization. This ectopic ossification is slowly progressive, and patients with OPLL can range from asymptomatic to severely myelopathic. The most common location of OPLL is the cervical spine followed by the thoracic spine, but it can also occur anywhere in the spinal axis. Ossification of the posterior longitudinal ligament is more frequently noted in male patients by a ratio of 2:1, and is more common in East Asian populations, particularly in the Japanese where it was first described. The incidence increases with age, with most cases occurring after 40 years of age. Previously, the inheritance patterns of OPLL were confined to familial studies and large-scale epidemiological studies to discern predisposing risk factors and possible Mendelian inheritance patterns. However, with the recent advances in genetic laboratory technology as well as the understanding and sequencing of the human genome, more specific studies to determine gene mutations involved in, predisposing to, and causing OPLL have been pursued. Analysis of contributing factors such as growth factors, transcription factors, and cytokines have also become possible with advances in cytochemical laboratory techniques. Taken together, this is a new era of understanding not only the inheritance of OPLL, but also its pathogenesis, natural history, and exacerbating factors.

**Object.** Ossification of the posterior longitudinal ligament (OPLL) is a pathological process of ectopic calcification with a preponderance for the cervical spine. Epidemiological and familial studies have both indicated predisposition; however, the genetic inheritance pattern and responsible genes for OPLL are still uncertain. The aim of this study was to evaluate and summarize the current understanding of the genetics underlying OPLL.

**Methods.** The authors reviewed epidemiological and genetic studies surrounding OPLL, with a particular focus on inheritance patterns and potential genes responsible for OPLL, using a PubMed database literature search.

**Results.** Despite an unclear inheritance pattern, there appears to be a strong familial link in patients with OPLL. Examination of these patterns using linkage analysis has shown multiple candidate genes that could be responsible for the inheritance of OPLL. Genes for collagen, nucleotide pyrophosphatase, transforming growth factors, and the vitamin D receptor have all been implicated. Additionally, multiple cytokines and growth factors, including bone morphogenetic proteins as well as other proteins and interleukins involved in bone development, have been shown to be abnormally expressed in patients with OPLL. In addition, multiple mechanical and metabolic factors such as hyperinsulinemia and obesity have been shown to be linked to OPLL.

**Conclusions.** Ossification of the posterior longitudinal ligament has a complex inheritance pattern. It does not appear that OPLL follows a simple, single-gene Mendelian inheritance pattern. Development of OPLL is more likely multifactorial in nature and develops in patients with a genetic predisposition from a variety of different mutations in various genes on various chromosomes. Additionally, environmental factors and interaction by other pathological disease processes, such as obesity and diabetes mellitus, may play a role in the development of OPLL in susceptible individuals. (DOI: 10.3171/2010.12.FOCUS10275)

**Key Words** • ossification of the posterior longitudinal ligament • genetic analysis • review

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**Abbreviations used in this paper:** BMP = bone morphogenetic protein; HLA = human leukocyte antigen; NPPS = nucleotide pyrophosphatase; OPLL = ossification of the posterior longitudinal ligament; SNP = single nucleotide polymorphism; TGF-β = transforming growth factor–β; ZFR = Zucker fatty rat.
Methods

A comprehensive literature search was performed using the PubMed database for all journal articles published until October 2010. Key words used in the search included “ossification of the posterior longitudinal ligament,” “genetics,” “OPLL,” and “epidemiology,” terms were searched individually or in combination. The appropriate articles for our review were selected based on scientific investigations surrounding the genetic inheritance and susceptibility patterns of OPLL in humans and animal models. We limited our results to articles only in the English language.

Results

Familial Inheritance Pattern Studies

Initial inheritance studies of OPLL were limited to epidemiological investigations of the disease with a focus on familial prevalence. Overall, OPLL is considered to be more common in East Asian populations with a prevalence between approximately 2% and 4%, which is markedly more common than in the US and Europe, where prevalence is roughly 0.01%–2%. Studies in twins have shown that OPLL tends to involve analogous types of pathological ossification, and point toward genetic rather than environmental factors as influencing development of OPLL. Furthermore, the prevalence of OPLL has been shown to be much greater among family members of patients with OPLL. Terayama studied 347 patients with OPLL and their families, and found that OPLL was found in approximately 26% of the patients’ parents and in 28% of the patients’ siblings, indicating a strong familial predisposition to OPLL. This finding was troubling, given that the inheritance patterns were not consistent with either a classic autosomal dominant or recessive pattern of inheritance. The authors concluded that OPLL was likely explained by a single gene inheritance, and that given the late-onset of OPLL, the most likely mode of inheritance was actually autosomal dominant inheritance with incomplete penetrance. In contrast, Hamanishi et al. examined a single family in detail and determined that OPLL inheritance in this family was consistent with autosomal recessive inheritance patterns. From such familial studies, it is clear that OPLL has a strong genetic inheritance; however, the pattern of genes responsible for this inheritance is uncertain.

Association of OPLL to HLA Haplotypes and Examination of Chromosome 6

In 1991, Sakou et al. studied 33 families of patients with OPLL and examined the HLA haplotypes of these families. They found that there were 6 HLA haplotypes that were observed frequently in that population, and 3 of these haplotypes were found to be exceedingly rare in the general Japanese population, suggesting an association of OPLL and these rare haplotypes. Moreover, it was found that the relatives of patients with OPLL who also had OPLL tended to have both identical HLA haplotypes, whereas relatives without OPLL had only 1 shared HLA haplotype. This study indicated that OPLL inheritance was genetic, given that an individual inherits 1 HLA gene set from each parent, and the relatives of patients with OPLL who also had OPLL tended to have identical HLA haplotypes. Furthermore, the authors concluded that the gene responsible for OPLL would likely fall on the same chromosome that coded HLA (chromosome 6). These results were later confirmed in a study of 24 patients and 61 sib-pairings, in which relatives with 2 HLA haplotypes had greater than a 50% chance of having OPLL, and those with only 1 identical strand were shown to have less than a 25% chance.

Following these findings, a search for the gene responsible for OPLL on chromosome 6 was undertaken. Koga et al. analyzed 91 affected sib-pairs using genetic linkage and found that the gene for collagen IIA2 (COL1IA2 encoding the α2 chain of type XI collagen), near the HLA complex, showed a strong linkage. Of the 19 gene variants found, 4 revealed a statistically significant likelihood of association with OPLL. These findings were supported by further research by the same group in which they found that a polymorphism of intron 6 (-4A) resulted in an alteration of the splicing of the COL1IA2 transcript, offering more evidence that COL1IA2 was in fact the gene responsible for OPLL. Specifically, they found that retention of certain exons (exon 7) combined with loss of another exon (exon 6) within this intron was associated with a lower probability of OPLL, perhaps conferring a protective role. Another study examining the COL1IA2 gene from 161 patients with OPLL revealed 5 frequent SNPs from which likelihood ratios were able to construct potential haplotypes. Of these, the most commonly noted haplotype was found to be more frequent in male patients. The authors believed this to be congruous with the known prevalence of OPLL in males (at a 2:1 ratio to females in epidemiological studies), and concluded that this demonstrated further evidence that COL1IA2 was the gene behind OPLL.

Large-Scale Screening Studies for Candidate Genes in OPLL

Despite all the evidence that pointed toward COL1IA2 as a gene responsible for OPLL, several groups continued to search for additional and alternative genes responsible for OPLL. Tanaka et al. conducted a genome-wide linkage analysis of 142 sib-pairs and detected linkage on 6 different chromosomes, with the strongest linkage on 21q, far away from the locus of COL1IA2. In total, 4 genes were identified in the linkage area noted. Single nucleotide polymorphism linkage disequilibrium testing was performed, revealing that COL6A1 (encoding the α2 chain of type VI collagen) was the gene that was most closely related to OPLL. Polymorphisms of this gene were further found to be related to diffuse idiopathic skeletal hyperostosis in the Japanese population (another related disease process of pathological ossification), as well as OPLL in the Chinese (and not just the Japanese) population. These studies provided additional evidence that COL6A1 not only played a strong role in OPLL, but in pathological ectopic ossification in general. Likewise, Furushima et al. studied 88 candidate genes, including
Genetics of ossification of the posterior longitudinal ligament

**COL11A2** and multiple genes known to be involved in the ossification process, and found no association with OPLL with any except BMP4, which itself was only weakly linked.

Further study of genes near the HLA locus was pursued by the same team that described the initial linkage distal to the HLA complex. Numasawa et al. examined the retinoic X receptor β (RXRβ) locus in 134 patients, as this gene was noted to be adjacent to COL11A2 in the murine and human genomes on chromosome 6 near the HLA locus. They discovered 3 variants, 2 of which showed a strong association with OPLL, suggesting that this gene and its location on chromosome 6 may be associated with the inheritance of OPLL.

Other groups have investigated the vitamin D receptor gene as a potential link to OPLL. One group found that the B allele occurred much less frequently in patients with ossification of spinal ligaments in general than controls, implicating that 1) the vitamin D receptor gene (RXRβ) could play a role in inheritance of OPLL, and 2) that the B allele may act as an inhibitor of ossification. Along the same lines, another group noted that a certain SNP of the vitamin D receptor gene (FokI variant) was connected to OPLL in comparison with controls. They found that the FF genotype was strongly associated with OPLL (while the F allele is protective), further suggesting a role for the vitamin D receptor gene in the inheritance of OPLL.

**Animal Models of OPLL: Insight Into Inheritance and Pathogenesis of OPLL**

Since Hosoda et al. first described the tiptoe walking (twy) mouse, it has been used as an animal model for OPLL. This naturally occurring mutant mouse has pathological ossification of the spinal ligaments similar to OPLL that results in progressive myelopathy and paraparesis. In an effort to determine the human locus of a gene responsible for OPLL, several groups attempted to find the murine gene responsible for twy. Okawa et al. first localized the gene to a small segment on murine chromosome 10, and then they were able to determine that the gene responsible was NPPS, a gene encoding NPPS, which was mutated in twy resulting in a stop codon. Since NPPS was known to be an inhibitor of calcification, the gene encoding this enzyme seemed a plausible candidate gene for not only twy but also OPLL. Therefore, 323 patients with OPLL were screened for SNPs of NPPS, and 2 SNPs were found solely in patients. After further study, Nakamura et al. were able to determine that a deletion in the vzig allele occurred in a significantly greater percentage of OPLL patients than in controls, indicating that human NPPS and the gene encoding it (NPPS) likely played a strong role in the genetics of OPLL. Furthermore, it has been shown that a different SNP in human NPPS resulted in not only increased propensity toward OPLL, but also increased severity of OPLL.

The ZFR is a murine model that was originally used for obesity, hyperinsulinemia, hypercholesterolemia, and hyperlipidemia. However, it was noted that these mice had orthotopic ossification of spinal ligaments and that this ossification is histopathologically similar to human OPLL. Therefore, ZFRs have been proposed as, and subsequently used as, a model for OPLL. Since the leptin receptor gene is known to be the mutated gene in the ZFR model, serum leptin levels were analyzed in patients with spinal ligament ossification and compared with controls. It was found that females with ossified spinal ligaments (such as OPLL) had significantly higher serum leptin levels and insulin levels than controls, suggesting that leptin and the leptin receptor gene may play a role in the inheritance and pathogenesis of OPLL. Further study has shown that SNPs of NPPS and the leptin receptor gene are not necessarily related to OPLL, but rather that polymorphisms of the genes for NPPS and the leptin receptor gene are associated with greater severity of OPLL.

**Exogenous Factors May Contribute to OPLL**

While the aforementioned studies point toward a strong genetic component in the development of OPLL, multiple studies have shown that various exogenous and modifiable risk factors may also contribute to the development of OPLL. Kobashi et al. administered questionnaires to 69 patients with OPLL and found that obesity, diabetes mellitus, and lumbago were independent risk factors for OPLL. Additionally, a family history of myocardial infarction, limited intake of vegetables and salads, and even long working hours have been noted as independent risk factors. The role of hyperinsulinemia itself was studied by Li et al., who noticed that high concentrations of insulin promoted BMP-2 to induce alkaline phosphatase expression/activation, which could in turn indirectly induce osteogenic differentiation.

Mechanical stretch has also been proposed as a contributing factor in the pathogenesis of OPLL; however, that mechanism has not been well described. Tanno et al. demonstrated that cyclic stretching on cultured spinal ligaments increased expression of alkaline phosphatase, osteopontin, and several BMPs and BMP receptors. A similar study by Iwasawa et al. showed that endothelin and alkaline phosphatase expression was increased with mechanical stress in OPLL specimens, but not in non-OPLL specimens, suggesting that mechanical stress may promote ossification in susceptible cells.

**Cytokines and Transcription Factors**

With the development of better histochemical laboratory studies, multiple growth factors, cytokines, and transcription factors have been implicated in the inheritance and pathogenesis of OPLL. Kawaguchi et al. initially showed that BMP-2 and TGF-β were present in the ossified matrix of the posterior longitudinal ligaments of patients with OPLL and thus suggested that BMP-2 and TGF-β were important initiators in the ossification process in OPLL. Tanaka et al. later confirmed that the BMP-2 gene was expressed in spinal ligaments of patients with pathological ectopic ossification of the spinal ligaments (such as OPLL). Furthermore, they proved that BMP-2 presence activated alkaline phosphatase, which suggested that BMP-2 could have a direct causal role in ossification of spinal ligaments. Likewise, Kamiya et al. confirmed that an SNP in the TGF-β1 gene was more...
likely to be found in patients with OPLL. Others have shown that polymorphisms of the BMP-2 gene are associated with severity, as well as prevalence of OPLL. Horikoshi et al. demonstrated that an alternative TGFβ gene, TGFβ3, was found to have a significant association to OPLL (while many other previously implicated candidate genes, such as COL11A2, did not show significant association). Other growth factors, cytokines, and genes that have been shown to have increased expression or different polymorphisms between patients with OPLL and those without included purinoreceptors, osteopontin, CTGF/Hcs24, the estrogen receptor, and interleukin-1.

Discussion

Since the original studies demonstrating a strong familial tie to OPLL, the genetic contribution to the development of OPLL has been undeniable. The conflicting reports from these studies, with some suggesting that OPLL follows autosomal dominant inheritance while others suggest it follows autosomal recessive inheritance, point toward a complex inheritance pattern for OPLL. It seems most likely that OPLL follows neither classic autosomal dominant or recessive inheritance patterns.

A link between HLA and OPLL appears to be present, but an association of HLA with OPLL does not implicate causation. Many pathological disease processes are noted to be more frequent with a certain HLA type (diabetes, ankylosing spondylitis, and others). Similarly, the HLA haplotypes associated with OPLL in Sakou and Matsunaga’s studies may not be responsible for OPLL. Rather, it seems more likely that the HLA haplotypes noted to be associated with OPLL are only that—associated with an increased likelihood of a patient having OPLL.

While many groups have implied that COL11A2 is the gene responsible for OPLL, other groups have failed to find an association of COL11A2 with OPLL in their series, thus calling into question the role of COL11A2 in the inheritance of OPLL. It makes sense theoretically that a collagen gene could be responsible for OPLL, given collagen’s intimate relationship to bone formation. Therefore, it makes just as much sense that COL6A1 may be a contributing gene in OPLL, as is implicated in multiple other studies. This gene’s association does, however, negate the idea that the gene responsible for OPLL lies on chromosome 6 near the HLA locus. This idea assumes, however, that there is only 1 responsible gene for OPLL, an idea that seems less likely given the multitude of other genes implicated in various studies as being associated with OPLL inheritance. Given collagen’s intimate relationship to bone formation, it makes just as much sense that COL6A1 may be a contributing gene in OPLL, as is implicated in multiple other studies. This gene’s association does, however, negate the idea that the gene responsible for OPLL lies on chromosome 6 near the HLA locus. This idea assumes, however, that there is only 1 responsible gene for OPLL, an idea that seems less likely given the multitude of other genes implicated in various studies as being associated with OPLL inheritance (BMP-4, RXRβ, NPPS, and leptin receptor gene). Therefore, it seems most likely that OPLL has many potential genes involved in its inheritance, pathology, and expression. This would then also explain the inability of familial studies to explain the type of autosomal inheritance pattern (autosomal dominant vs recessive), as these studies also assumed a single gene inheritance pattern.

Additionally, it seems clear that multiple growth factors, cytokines, and transcription factors are involved in the pathogenesis, inheritance, and development of OPLL. Multiple polymorphisms in multiple genes of multiple bone modulating proteins have been linked to OPLL. It seems that with so many and so varied mutations noted, it is unlikely that there is only 1 growth factor gene responsible for OPLL. Rather, it seems most likely that any number of mutations in a variety of genes for growth factors, cytokines, and transcription factors may be associated with OPLL, and therefore predispose a patient for developing OPLL, even if there is no direct causation.

Finally, the interactions of both mechanical components as well as other disease pathologies have been linked to OPLL. Hyperleptinemia, hypothyroidism, obesity, and diabetes mellitus have all been linked to OPLL in both humans and mice (ZFR model). It is unclear, however, whether these states cause formation of OPLL, or whether they merely predispose patients to the development of OPLL. For example, not all patients with diabetes have OPLL, and not all patients with OPLL have diabetes. Therefore, it is difficult to associate a causation of diabetes to OPLL.

Likewise, mechanical stretch has been shown to induce expression of BMPs and endothelins to contribute to bone synthesis in susceptible OPLL cells, but not in controls. Again, direct causation cannot be attributed, as only susceptible cells (OPLL cells) show induced expression of BMPs with stretch. Rather, it seems that all these exogenous factors may contribute to the development of OPLL in susceptible individuals, but not in those without a predetermined susceptibility.

Ossification of the posterior longitudinal ligament likely demonstrates multifactorial inheritance. From the large number of genes that have been associated with OPLL (from many conflicting studies), it seems only logical that there are likely multiple genes involved in not only the inheritance, but also the pathogenesis of OPLL. Furthermore, varied exogenous factors have been noted to contribute to the development of OPLL. In all likelihood, there are in fact multiple exogenous factors that are not mutually exclusive contributing to development of the underlying disease process in susceptible individuals over a course of many decades before they actually develop symptoms.

Conclusions

The inheritance patterns of OPLL are extremely complex, given that very likely multiple genes are involved in the development of pathological ectopic ossification. There are also multiple exogenous factors that likely contribute to the pathogenesis of OPLL, but only in genetically susceptible individuals. Therefore, the inheritance of OPLL is best described as a multifactorial genetic inheritance.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Stetler. Analysis and interpretation of data: Park, Stetler. Drafting the article: Stetler. Critically revising the article:
Genetics of ossification of the posterior longitudinal ligament

Park. Reviewed final version of the manuscript and approved it for submission: Park, La Marca. Study supervision: Park, La Marca.

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