

Oral Lichen Planus Genetics Update

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ABSTRACT

Lichen planus is a chronic autoimmune multi-factorial inflammatory condition of the mucocutaneous skin that mainly interests the skin and oral mucosa. Oral Lichen Planus (OLP) affects 0.5 to 1% of the world's population and all human races equally. The factors that act as triggers of autoimmune processes and determine the appearance of OLP are represented by genetic predisposition, skin injuries, viral infections, contact allergies, and medications. OLP affects the oral mucosa and occurs frequently on the inside of the cheeks and less often on the edges of the tongue, gums, or lips. The condition is manifested by the appearance of painful erosions and mouth ulcers, accompanied by erythema and gingival scaling, and sometimes localized inflammation of the gums, near the amalgam fillings. There are 132 genes currently involved in the etiopathogenesis of OLP, but only a few appear to play a major role. These genes have been termed "leader genes". Thus, based on bioinformatics studies, the main genes involved in the pathogenesis of OPL are JUN, EGFR, FOS, IL2, and ITGB4. Although genetic status, immune system background, and infectious diseases are considered to be the most important incriminating and determining factors, the etiopathogenesis of OLP remains poorly known. Further genetic research is needed in order to achieve the generalizability of the findings and to strengthen the obtaining results.

Keywords: Oral Lichen Planus, genetic predisposition, "leader genes".

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I. INTRODUCTION

Lichen planus (LP), a chronic multi-factorial inflammatory condition of the mucocutaneous skin that mainly affects the skin and oral mucosa, is derived from the Greek word "leichen" which means tree moss, and the Latin word "planus" which means flat [1], [2].

The condition was first described in 1866 by the English physician Erasmus Wilson, who initially considered this disease to be the same disease as "lichen ruber planus", previously described by the Austrian dermatologist Ritter von Hebra [2].

In 1895, Louis Frédéric Wickham observed the characteristic reticulated white lines on the surface, today recognized as Wickham stripes, and Darier made the first formal description of the histopathological changes associated with LP [1], [2].

Later, in 1937, Guogerot and Burnier described the coexistence of oral, cervical, and stomach LP lesions, and in 1982, Pelisse and collaborators presented a similar variant of mucosal LP called the "vulvovaginal-gingival syndrome with erosive lesions", involving the oral and vulvovaginal mucosa [2].

II. EPIDEMIOLOGY

Oral Lichen Planus (OLP) affects 0.5 to 1% of the world's population and all human races equally [2]-[4]. OLP is not found in children.

OLP affects women, with the average age of onset being around 60 years [5].

III. ETIOPATHOLOGY AND PHYSIOPATHOLOGY BACKGROUND

Lichen planus is an autoimmune disease whose onset is due to the destructive action of helper T cells on the constituent proteins of skin cells and mucous membranes as a result of an exacerbated immune response [1].

The factors that act as triggers of autoimmune processes and determine the appearance of OLP are represented by genetic predisposition, skin injuries, viral infections (Hepatitis C Virus), contact allergies (Flat Lichen of the oral mucosa on contact with tissues with various materials used to make dental fillings), and medications (Gold Salts, Quinine, Quinidine, Captopril, Hydroxychloroquine), (Fig. 1), [2], [6].

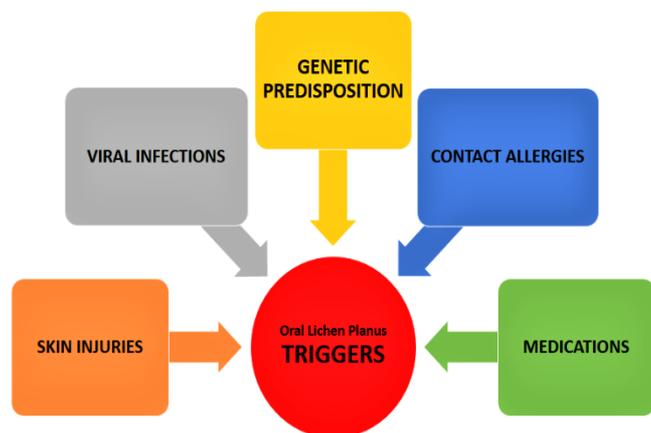


Fig. 1. Oral Lichen Planus triggers

IV. MAJOR CLINICAL MANIFESTATIONS

OLP affects the oral mucosa and occurs frequently on the inside of the cheeks and less often on the edges of the tongue, gums, or lips [7].

The condition is manifested by the appearance of painful erosions and mouth ulcers, accompanied by erythema and gingival scaling, and sometimes localized inflammation of the gums, near the amalgam fillings. After Gorouhi and collaborators, the clinical subtypes of OLP and the most common sites of involvement are presented in Figure 2 [2].

RETICULAR	ATROPHIC	HYPERTROPHIC	EROSIVE	BULLOUS	PLAQUE-LIKE
<ul style="list-style-type: none"> Buccal mucosa and mucobuccal folds Lateral and dorsal tongue Gingiva and lips 	<ul style="list-style-type: none"> Attached gingiva 	<ul style="list-style-type: none"> Buccal mucosa 	<ul style="list-style-type: none"> Lateral and ventral portions of tongue Buccal mucosa 	<ul style="list-style-type: none"> Posterior and inferior areas of buccal mucosa 	<ul style="list-style-type: none"> Dorsum of the tongue and buccal mucosa

Fig. 2. The clinical subtypes of Oral Lichen Planus and the most common sites of involvement.

V. DIAGNOSIS

The diagnosis of OLP is clinical and is established based on its manifestations, but in certain situations, it is necessary to perform additional investigations represented by:

- Skin biopsies that collect fragments of affected tissue for microscopic examination (examination of tissue fragments collected by excisional biopsy is a definite diagnosis of the condition that causes specific histological changes in the mucous membranes and skin) [1];
- Allergic Patch Tests in patients with gingival damage [8].

The anatomopathological characteristics of OLP are the following: epithelial hyperkeratosis with saw tooth rete ridges, basal epithelial cells atrophia or liquefaction degeneration, spinous epithelial cells atrophy or acanthosis, homogeneous eosinophilic material deposit in the epithelial connective tissue junction, and a band-like infiltrate of lymphocytes involving the superficial lamina propria [1], [2], [8].

VI. GENETICS UPDATE

Although genetic status, immune system background, and infectious diseases are considered to be the most important incriminating and determining factors, the etiopathogenesis of OLP remains poorly known [9].

Also, the physiopathology of OLP is complex, being the result of direct or indirect interaction of a large number of genes.

Polymorphisms in cytokine-encoding genes play a vital role in the management of the immunological response, leading to various functional scenarios, which in turn influence the outcome of the disease establishment and progression [10].

A. "Leader genes" of OPL

There are 132 genes currently involved in the etiopathogenesis of OLP, but only a few appear to play a

major role. These genes have been termed "leader genes." Thus, based on bioinformatics studies, the main genes involved in the pathogenesis of OPL are JUN, EGFR, FOS, IL2, and ITGB4 genes (Fig. 3), [11].

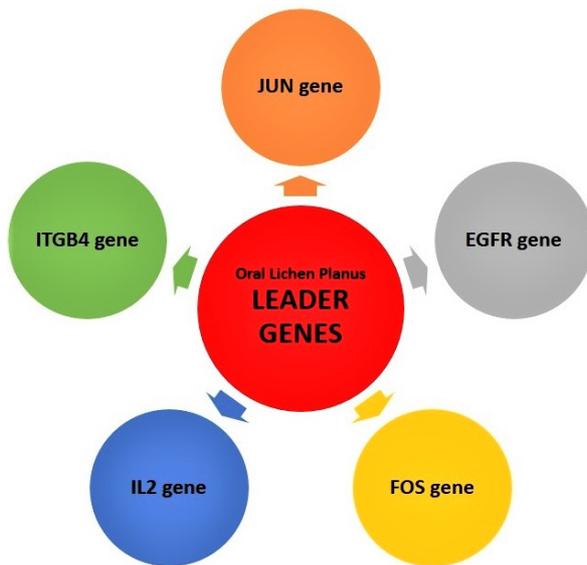


Fig. 3. "Leader genes" of Oral Lichen Planus

B. JUN Gene

Transcription factor JUN is a protein that in humans is encoded by the JUN gene. JUN gene encodes a protein that is highly similar to the viral protein, which interacts directly with specific target DNA sequences to regulate gene expression. This gene is intronless and is mapped to 1p32-p31, a chromosomal region involved in both translocations and deletions in human malignancies [11].

C. EGFR Gene

The epidermal growth factor receptor (EGFR) is a transmembrane protein that is a receptor for members of the epidermal growth factor family (EGF family) of extracellular protein ligands [11], [12]. EGFR gene is mapped to the 7p11.2 chromosomal region.

D. FOS Gene

The FOS gene family consists of four representatives: FOS, FOSB, FOSL1, and FOSL2. These genes encode leucine zipper proteins that can dimerize with proteins of the JUN family gene, thereby forming the transcription factor complex AP-1. As such, the FOS proteins have been implicated as regulators of cell multiplication, differentiation, and conversion. In certain circumstances, the expression of the FOS gene has also been linked with the apoptosis of cells. FOS proto-oncogene is mapped to the 14q24.3 chromosomal region [13].

E. IL-2 Gene

The cytokine secreted by the IL2 gene plays a very important role in the proliferation of B and T lymphocytes [11].

F. ITGB4 Gene

ITGB4 (Myc-DDK-tagged)-Human Integrin, Beta 4 (ITGB4) gene encodes a receptor for the laminin,

respectively, the beta 4 subunit of a protein known as an integrin. ITGB4 gene is mapped to the 17q25.1 chromosomal region [11], [14].

G. VDR Gene

VDR gene encodes the Vitamin D receptors (VDRs), which play a crucial role in the coordination of the functions of vitamin D [15].

Genetic alterations of this gene are associated with the predisposition to OLP. Also, rs2239185 and rs7975232 may be considered the genetic markers for the susceptibility to OLP in the Han population of China. The location of the VDR gene is a 12q12–14 chromosomal region [16].

H. IL-1 β Gene

IL-1 β gene in OLP, respectively the polymorphism IL-1B +3953C/T, rs1143634, was associated with the susceptibility to other comorbidities, like chronic periodontitis and type 1 diabetes mellitus [10].

On the other hand, IL-1 β , a specific pro-inflammation cytokine, is the most linked with oral carcinogenesis [17].

I. IL-6 Gene

Xu and collaborators observed that OLP-associated fibroblasts and normal fibroblasts produced significant amounts of IL-6 in the presence of inflammatory factors [18].

Thus, they concluded that anti-IL-6 receptor antibodies and the target of PLO-associated fibroblasts may help the new therapeutic factors to suppress the malignant transformation of PLO [18].

J. IL-18 Gene

Analytical and statistical investigations using logistic regression highlight that polymorphic locus rs187238 in the IL-18 gene is linked with the predisposition of LP development in a recessive model ($p=0.042$). In addition, the association of a polymorphic locus rs187238 in the IL-18 gene with the recurrence risk was described: rs187238*C/C genotype is a genetic biomarker of increased risk of OLP recurrence ($p=0.01$), [19].

K. TNF- α Gene

The gene polymorphisms of TNF α has been reported to affect the susceptibility and the progression of OLP. A meta-analysis suggests that the substitution of G to A of TNF α – 308 G/A polymorphism is a risk factor for OLP. Its effect exists among mixed populations with mixed HCV status. Also, the TNF α –308 G/A polymorphism may be a useful genomic marker for OLP [20].

L. FAM3B Gene

Wang and collaborators found that the downregulation of the FAM3B gene was particularly linked with the appearance and evolution of OLP.

FAM3B gene was under-expressed in OLP relative to normal humans and further substantially downregulated in the oral squamous cell carcinoma (OSCC) in comparison with OLP.

Also, FAM3B could be also associated with the initiation and malignant evolution of OLP and might be a potential predictive biomarker for OLP [9].

M. IFN- γ Gene

Interferon-gamma (IFN- γ), a soluble cytokine, respective a dimerized glycoprotein, the single member of the type II class of interferons, is an important activator of macrophages and inducer of major histocompatibility complex class II molecule expression [21].

The location of IFN- γ gene is in the 12q15 chromosomal region. Aberrant IFN- γ expression is associated with a number of autoinflammatory and autoimmune diseases [21].

Regarding OLP, Al-Mohaya and collaborators concluded that the polymorphism IFN- γ (874A/T) is linked with the predisposition to develop the disease [22].

Ya-Qin Tan and collaborators, in another study, using an autophagy array technology complex, analyzed the mRNA expression of autophagy-related genes in peripheral T cells of OLP patients [23].

The results highlight an upregulation of IGF1 expression on T cells in a gender-associated and age-dependent manner and a distinct expression model of ATG9B between diverse clinical aspects, which may indicate the importance of autophagy in the immune reaction of OLP [23].

N. Cat-B and Cav-1 Genes

OLP confers a 1% risk of transformation to OSCC [24]. Alterations in DNA damage response and apoptosis pathways underlie OLP-related OSCC transformation and are supported by mutational signatures indicative of DNA damage [24].

The study of Xie and collaborators, characterized patterns of mutational events present in OLP associated with squamous cell carcinoma and in squamous cell carcinoma associated with OLP but not in non-transforming OLP [24].

Increased gene expression of Cathepsin-B (Cat-B) and Caveolin-1 (Cav-1) gene in OSCC has been linked with an increase in the stage and grade of malignancy [25].

Therefore, Pakfetrat and collaborators examining these expressions, predicted the biological behavior of OSSC as well as the probability of neoplastic transformations of OLP [25], [26].

Because the gene expression of Cat-B and Cav-1 increases in OLP and OSCC compared to controls, it can be concluded that these two markers are involved in both OSCC malignancy and precancerous pathophysiology, such as OLP [25].

O. Familial OLP

Pathogenesis of multifactorial diseases involves the integration of genetic and environmental factors over time [27]-[29].

Wang and collaborators, using OLP family samples, performed whole-genome genetic linkage analysis and identified the disease locus of chromosome 3p14-3q13 region, where one mutation may be responsible for familial OLP. This finding would also suggest that a novel gene in the chromosome 3p14-3q13 region may play a role in the pathogenesis of OLP [30].

VII. CONCLUSION

OLP is a very common condition in dental practice. Identifying the cause that leads to OLP is essential for

treatment, especially in the case of reaction to materials used in dentistry, for which the therapeutic course begins with the removal of the causal factor.

Both the etiology and the pathogenesis are complex and incompletely elucidated, requiring more research, especially due to the risk of malignant transformation.

However, further genetic research with a large sample size involving different ethnic populations is needed in order to achieve the generalizability of the findings and to strengthen the obtaining results.

AUTHORS' CONTRIBUTION

All authors contributed equally to the first author, in the preparing, reviewing, and editing of the article.

All authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

STATEMENT OF INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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