

Association between genetic factors and periodontal diseases in some populations

Shaghayegh Pishkari*, Jalaloddin Hamissi**, Adeleh Ghoudosi***, Salma Tabatabaei****

* Post graduate student of Genetics

**Associate Professor, Department of Periodontology, School of Dentistry, Qazvin University of Medical Sciences, Qazvin, Iran.

***Department of Biostatistics, College of Medicine, Qazvin University of Medical Sciences, Qazvin, Iran.

****Dentist

Abstract

Introduction: GAgP is a multifactorial disease, which occurs in presence of bacteria and is influenced by genetic and environmental factors; leading to periodontal tissue dysfunction among subjects younger than 30 years. Proinflammatory cytokines are involved in immune response to periodontal pathogens through associating in inflammation phenomenon. It is supposed that gene polymorphisms of cytokines play a role in immune response and therefore in periodontal pathogenesis. Recent studies have suggested polymorphism in the interleukin gene association with periodontitis.

Materials & Methods: In this review article we study a literature review of all researches in last 3 years in some population about suggested polymorphism in the interleukin genes association with periodontitis.

Results & Conclusion: The lack of any association between IL1 β +3953, IL1 β 3962, TNF α 308, IL1 β -511 IL1RN(VNTR), IL1RN8006, IL10-1082, IL1RN-2018 IL1 α -889, IL1 β -35, IL1-RN9589, IL1RN11100, IL1 β +3954 the polymorphism and periodontitis in presented populations, bring into doubt the usefulness of these candidate gene as marker of susceptibility of periodontitis. And 1363 IL6-174, IL4-1098, IL4-33, TNF α -308, IL6- IL1RN, IL1 β -511, IL1RN VNTR, IL1RN 8006 polymorphisms are the risk marker for periodontitis.

Key words: Polymorphism, Interleukin, periodontal disease.

Introduction:

Periodontitis is a multifactorial disease which occurs in presence of bacterial plaque. However, the spread and the severity of the disease depend on environmental factors, acquired diseases and genetic susceptibility. Periodontal tissue destruction,

tooth mobility and tooth loss are the most important complications of this disease (18). In addition to bacterial pathogens, the immune responses against bacterial attack are crucial in gingival inflammation. Cytokines which have regulatory effects on immune responses, play an important role.

Like other cellular factors, since the productions of various cytokines are carried by genes, the status of these genes can indirectly affect the severity of the gingival disease (14). Interleukins are of most important members of cytokines. Interleukin 10 (cytokines release inhibitory factor) is secreted by T helper 2 and active macrophages, and prevents the production of the most or all of the cytokines secreted by T helper 1. Therefore, immune system and genetic factors are essential in pathogenesis of periodontal disease and mutation in the promoter region of the genes can actually affect their production. Patients with gingivitis and polymorphism of interleukin 10 are more susceptible to periodontitis (9). The most important pro inflammatory cytokines are IL₁ α , IL-1 β and TNF α which have similar and synergistic effects. Furthermore, regulation of coagulation system and suppression of bone marrow stem cells can cause fever (24). In addition to inflammatory cell chemotaxis, TNF α , also stimulates the synthesis of IL₁, IL₆, IL₈ and increased production of T and B lymphocytes. Pro inflammatory cytokines increase the inflammatory cells such as neutrophils, monocytes and fibroblasts and cause vasodilatation, chemotaxis and inflammation (24, 30). TNF α is the most important host response against the active component of gram negative bacteria (i.e. LPS or endotoxins) which is produced by uni-nuclear phagocytes and it is increased by stimulation of gamma interleukins, IL₁ and IL₁₇. They are also produced by antigen activated T lymphocytes, activated natural killer cells (NKC) and activated monocytes. Since periodontitis is a multifactorial disease

with an inflammatory nature, hypothesis of genetic similarity with many other auto immune and inflammatory diseases such as asthma, atopy, lupus, arthritis have been proposed (19). Hence, we decided to review the previous researches done in this area to investigate the association between periodontal disease and its impact on the individual genetic problems.

Methods and materials:

In this study, all the previous researches investigating the relationship between polymorphisms in interleukin genes and periodontitis in different populations in recent 3 years have been reviewed.

Nibiali et.al, conducted a study in 2009 in which he investigated the relationship between various interleukin 6 genes and periodontitis. In this study he discovered that genotype -174GG and -136GG are periodontal disease risk factor in whites, however, such relation was not observed between genotypes and periodontitis in blacks and Asians.(25)

In 2010, Baradaran Rahimi et al studied the Association of Interleukin-1 Receptor Antagonist Gene Polymorphisms with Generalized Aggressive Periodontitis in an Iranian population in Mashhad-Khorasan. He observed that genotype A1A2 was significantly lower in control group comparing to test group, on the other hand A1A1 genotype and frequency of A1 allele were significantly higher in control group. Moreover the frequency of A1 allele was

totally different between the patients and healthy subjects meaning that it was higher in patient groups. As a result, genotype IL1RN and frequency of allele RN-IL1 was significantly different between the healthy subjects and patients with periodontal disease. (4)

In 2011, Ricci et al Found that there was a significant relationship between genotype TNF α _308 and periodontal disease, but no relation was found between periodontal disease and interleukins IL1RN-2018, IL1B-511, il1b-3954 genotypes. (27)

In 2011, Travilatto's study entitled "Association of IL1 gene polymorphisms with chronic periodontitis in Brazilians", no association was found between polymorphism of ILB (+3954) and IL1A (-889) genes and incidence of periodontal disease, however the presence of allele T in IL1B (-511) had an impact on periodontal disease in African Americans and black hybrids and genotype 2/2 of ILRN was associated with severe periodontal disease. As a result allele 2/2 in IL1RN of Brazil total population and allele T in IL1B-511 in an African American and black hybrids considered to be a risk for chronic periodontitis (31).

In 2007, Mellati in his research entitled ".Analysis of-1082 IL-10 gene polymorphism in Iranian patients with generalized aggressive periodontitis" concluded that there was no significant difference in genotype frequency between patients and controls. Additionally, the allele's frequency in the both groups showed no significant difference. so we conclude that there is no relation between the nucleotide

polymorphism at IL10_1082 position and incidence of aggressive periodontitis. (21)

In a study which was conducted by Ebadian et al, in 2009, the polymorphism of pro inflammatory cytokine genes was analyzed. His observation showed that the difference between IL_1 β polymorphism in position 3454, IL_1 α (-889) and TNF α (-308) and aggressive periodontitis, both in terms of genotype and allelic difference were not statistically significant. Therefore it can be concluded that 3954, IL-1 α (-889) and TNF α (-308) polymorphism cannot be considered as markers to determine genetic susceptibility to aggressive periodontitis, in Iranian-Khorasani population. (10)

In 2009, Kiani et al discovered that there was no association between IL_1 α (-889) polymorphism and periodontitis and presence or absence of allele 1 and allele 2 has no effect on periodontal disease. (16)

In 2011, Schulz et al studied the relation between Single nucleotide polymorphisms in interleukin-1 gene cluster and sub gingival colonization with *Aggregatibacter actinomycetemcomitans* in patients with aggressive periodontitis. He observed that there is no association between the IL1B and 3962, IL1a-889 and aggressive periodontal disease. (28)

In 2011, Karasneh et al, found that there is an association between chronic periodontal disease and polymorphism of IL-1RN (8006) and IL-1RN VNTR genes, however no relation was found between such polymorphism and aggressive periodontitis. No association was found between polymorphism of, IL1-RN9589, IL-1 α -889,

IL-1 β +3953, IL1 β -511, and IL1 β -35 IL1-RN11100 genes and periodontal disease as well. (15)

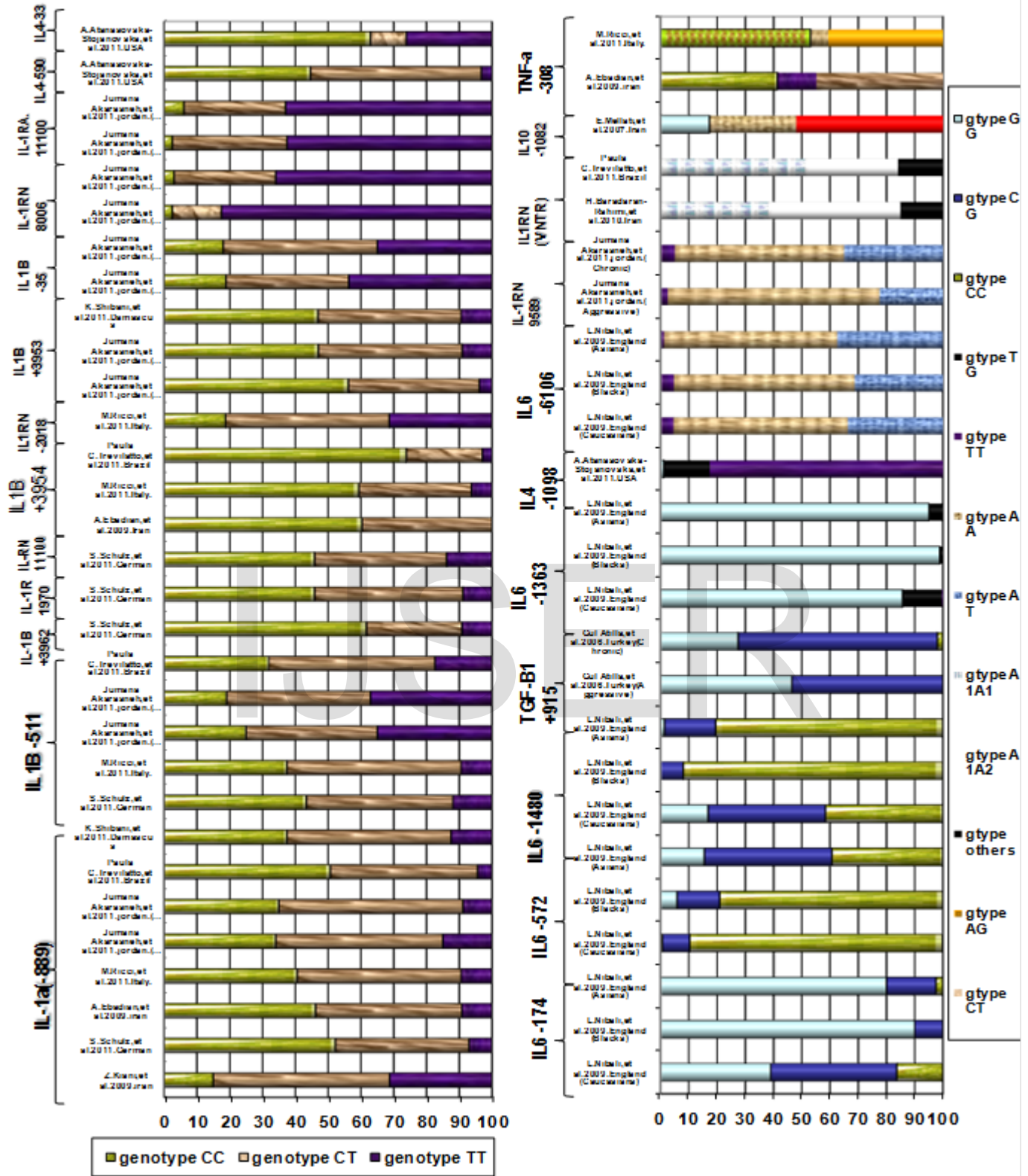
In 2011, Shibani et al in his study entitled “Analysis of IL-1 α (-889) and IL-1B (+3953) Gene Polymorphism in Syrian Patients with Aggressive Periodontitis” discovered no association between such polymorphisms and periodontal disease. This gene had no effect in presence of aggressive periodontal disease. (29)

In 2011, Atanasovka et al concluded that polymorphism of IL4-33, IL4-1098 has strong association with incidence of periodontal disease in Macedonian population. (2)

Results and conclusion:

High level of cytokines may be present in GCF and periodontal tissues and affect the periodontal tissue and bone destruction. Therefore, polymorphisms in these cytokines and their receptors can be considered as candidates in periodontal disease susceptibility (11). In studies like Ebadian's and McGuire's, loss of teeth in individual with IL_1 β , was reported to be 2.7 times more than those without the polymorphism (22). Meisel et al also discovered significant association between tooth loss and IL-1 β polymorphism. (11)

IJSER



Wagner also discovered association between IL₁β (3954), IL₁α (-899) and chronic periodontitis. (36)

Tabibzadeh found a relation between IL₁β and periodontal tissue destruction (34). Kiani found no relation between absence or presence of allele 1 and allele 2 and periodontal destruction

(16). However, in studies such as those of Armitage, polymorphisms of IL-1β and IL₁α in periodontitis and healthy subjects were not different (1). The results of the study which was led by Khoshhal et al in 2011 in Hamedan was quiet similar to results obtained in Donatie 's study on Swedish Caucasians in 2005 in which the distribution of genotype frequencies of IL₄Rα was not significantly different in test-control groups(8,17). But in Gonzales's study in 2007, the presence of single nucleotide polymorphism in position -590, -34 showed significant statistical difference between aggressive periodontitis and healthy individuals (13). In 2011, Atanasovska-Stojanovska observed significant relation between polymorphism of cytokine IL₄₃₃, IL₄₁₀₉₈ and chronic periodontitis in Macedonian population (2).

In 2011, in Tervilatto study, no association was found between polymorphism of ILB (+3954) and IL1A (-889) genes and incidence of periodontal disease, however the presence of allele T in IL1B (-511) had an impact on periodontal disease in African Americans and black hybrids and genotype 2/2 of ILRN was associated with severe periodontal disease. As a result allele 2/2 in IL1RN of Brazil total population and allele T in IL1B-511 in an African American and

black hybrids considered to be a risk for chronic periodontitis (31). Nibiali et.al, in their study in 2009 discovered that genotype -174GG and -136GG are periodontal disease risk factors in whites, but such relation was not observed between genotypes and periodontitis in blacks and Asians (25). In a study which was led by Radvar in 2008, it was observed that level of IL-6 was significantly higher in individuals with sever chronic periodontal disease comparing to healthy individuals (26). In Baradarane Rahimi's study in 2010 in Iran, genotype IL1RN and frequency of allele RN-IL1 was significantly different between the healthy subjects and patients with periodontal disease (4). Ricci et al studies show that there is a significant relationship between genotype TNFa₃₀₈ and periodontal disease, but there is no relation between periodontal disease and interleukins IL1RN-2018, IL1B-511, il1b-3954 genotypes (27). Mellati observed no relation between the nucleotide polymorphism at IL10₁₀₈₂ position and incidence of aggressive periodontitis (21). Ebadian in Mashhad (Khorasan) concluded that the difference between IL₁β polymorphism in position 3454, IL₁α (-889) and TNFa (-308) and aggressive periodontitis, both in terms of genotype and allelic difference were not statistically significant (10). Kiani et al discovered no association between IL₁α (-889) polymorphism and periodontitis and presence or absence of allele 1 and allele 2 has no effect on periodontal disease (16). Schulz et al found no association between the IL1B_{and3962}, IL1a-889 and aggressive periodontal disease (28). Karasneh et al, in Jordan, found that there is association

between chronic periodontal disease and polymorphism of IL-1RN (8006) and IL-1RN VNTR genes, however no relation was found between such polymorphism and aggressive periodontitis. No association was found between polymorphism of, IL-1RN9589,IL-1 α -889,IL-1 β +3953,IL1 β -511 , IL1 β -35 IL1- RN11100 genes and periodontal disease as well (15). Atanasovka et al concluded that polymorphism of IL4-33, IL4-1098 has strong association with incidence of periodontal disease in Macedonian population (2).

According to the studies reviewed, we can conclude that due to the lack of association between polymorphisms of,IL1 β +3953,IL1 β 3962, TNF α 308,IL1 β -511,IL1RN(VNTR),IL1RN8006,IL10-1082,IL1RN-2018IL1 α -889,IL1 β -35,IL1-RN9589, IL1RN11100 , IL1 β +3954 genes and periodontitis in communities studied, using these genes as risk markers in different periodontal diseases is questionable. On the other hand, polymorphism of 1363 IL6-174, IL4-

1098,IL4-33,TNF α -308 , IL6- IL1RN,IL1 β -511,IL1RN VNTR,IL1RN 8006 genes is proposed as a risk marker in diagnosis of periodontal diseases.

The most important cause of the difference in results of these studies could be due to racial differences (10), since racial differences play a crucial role in susceptibility to periodontal disease. The difference between allele frequencies in different populations explains the necessity of conduction of similar studies (33). the advantages of the association between genetic factors and periodontal disease can be as followings: Early diagnosis in patients who are at risk due to genetic factors, they may be subjected to preventive treatments, finally identification of the young people who do not have periodontitis but are at risk of sever periodontics due to genetic factors. Such individuals can be treated quickly and more effectively to be immune from progressive nature of the disease (17).

References

1. **Armitage, G.C., et al., 2000.** *Low prevalence of a periodontitis-associated interleukin-1 composite genotype in individuals of Chinese heritage. J Periodontol.* 71.2: 164-71.
2. **Atanasovska-Stojanovska. A, et al., 2011.** *IL4 gene polymorphisms and their relation to periodontal disease in a Macedonian population. Human Immunology.* 72.5: 446–450.
3. **Babel, N., et al., 2006.** *Analysis of tumor necrosis factor α , transforming growth factor- β , interleukin-10, IL-6 and interferon- γ gene polymorphisms in patients with chronic periodontitis. J Periodontol;* 77.12: 1978-83.

4. **Baradaran-Rahimi, H., et al., 2010.** Association of Interleukin-1 Receptor Antagonist Gene Polymorphisms with Generalized Aggressive Periodontitis in an Iranian Population. *J Periodontol.* 81:1342-1346.
5. **Behfarnia, P., et al, 2009.** Interleukin 17 and the pathogenesis of periodontal disease. 9th Annual Congress of Iranian Academy of Periodontology 9- 11 December. Tehran – Iran.
6. **Dashash, M., et al., 2005.** The relationship between interleukin-10 gene polymorphism at position-1082 and susceptibility to gingivitis in children. *J Periodontol.* 76.9: 1455-62.
7. **Dashash, M., et al., 2006.** Interleukin-10 haplotype frequencies in children with gingivitis. *J. Periodontol.* 77.9: 1503-9.
8. **Donati, M., et al., 2005.** Association of the -159 CD14 gene polymorphisms and lack of association of the -308 TNFA and Q551R IL-4RA polymorphisms with severe chronic periodontitis in Swedish Caucasians. *J Clin Periodontol.* 3.5:474-479.
9. **Dashash, M., et al., 2005.** The relationship between interleukin-10 gene polymorphism at position-1082 and susceptibility to gingivitis in children. *J Periodontol.*; 76.9: 1455-62.
10. **Ebadian, A.R., et al., 2009.** Analysis of Proinflammatory Cytokines Gene Polymorphisms in Generalized Aggressive Periodontitis (GAgP). *J Mash Dent Sch.* 33(3): 231-40.
11. **Galbraith, G.M.P., et al., 1999.** Polymorphic cytokine genotypes as markers of disease severity in adult periodontitis. *J Clin Periodontol.* 26.11: 705-9.
12. **Gonzales, JR., et al., 2004.** Interleukin-4 gene polymorphisms in Japanese and Caucasian patients with aggressive periodontitis. *J Clin Periodontol.* 31.5: 384- 389.
13. **Gonzales, JR., et al., 2007.** Single-nucleotide polymorphisms in the IL-4 and IL-13 promoter region in aggressive periodontitis. *J Clin Periodontol.*; 34.6:473-479.
14. **Gonzales, JR., et al., 2007.** Single-nucleotide polymorphisms in the IL-4 and IL-13 promoter region in aggressive periodontitis. *J Clin Periodontol.*; 34.6:473-479.
15. **Karasneh, J.A., et al. 2011.** Investigation of the interleukin-1 gene cluster polymorphisms in Jordanian patients with chronic and aggressive periodontitis. *Archives of oral biology* 56; 269 – 276.
16. **Kiani, Z., et al., 2009.** Polymorphism of IL-1 α (-889) Gene and Its Association with Aggressive Periodontitis. *Iran J Allergy Asthma Immunol.* 8.2: 95-98.
17. **Khoshhal, M., et al., 2011.** Association of Interleukin-4 Receptor Gene Polymorphism with Chronic Periodontitis. *Sci J Hamadan Univ Med Sci* ; 18. 3:63-69.

18. **Kinane, DF., Shiba, H., et al., 2005.** *The genetic basis of periodontitis, periodontal 2000.* 39: 91-117.
19. **Kinane, DF. et al., 1999.** *Analysis of genetic polymorphism at interleukin-10 and tumor necrosis factor F loci in early-onset periodontitis.* *J Periodontal Res.*34.7:379-386.
20. **Michalowicz, BS. 1994.** *Genetic and heritable risk factors in periodontal disease.* *J Periodontol;* 65. 5:479-488.
21. **Mellati.E, et al., 2007.** *Analysis of-1082 IL-10 gene polymorphism in Iranian patients with generalized aggressive periodontitis.* *Med Sci Monit.* 13.11: 510-14.
22. **McGuire, MK., Nunn, ME., 1999.** *Prognosis versus actual outcome. IV the effectiveness of clinical parameters and IL-1 genotype in accurately predicting prognoses and tooth survival.* *J Periodontol.*70.1: 49-56.
23. **Meisel, P., et al., 2002.** *Smoking and polymorphisms of the interleukin-1 gene cluster (IL-1 α , IL-1 β , and IL-1RN) in patients with periodontal disease.* *J Periodontol.* 73.1: 27-32.
24. **Mariette, X., et al., 2003.** *Anti-cytokines in the treatment of inflammation. Rev Part;* 53.5: 507-11.
25. **Nibali, L., et al.2009.** *Association between periodontitis and common variants in the promoter of the interleukin-6 gene.* *Cytokine* 45; 50–54.
26. **Radvar, M., et al., 2008.** *The Effect of periodontal Treatment on IL-6 production of peripheral Blood Monocytes in Aggressive Periodontitis and Chronic Periodontitis Patients.* *Iran.J.Immunol.* 5 .2:100-106.
27. **Ricci.M, et al.2011.** *Association between genetic risk score and periodontitis onset and progression.* *Archives of Oral Biology* 5 6 (2 0 1 1) 1 4 99 – 1 50 5.
28. **Schulz.S, et al.2011.** *Single nucleotide polymorphisms in interleukin-1 gene cluster and subgingival colonization with *Aggregatibacter actinomycetemcomitans* in patients with aggressive periodontitis.* *Human Immunology* 72; 940-946.
29. **Shibani.K, et al.2011.** *Analysis of IL-1 α (-889) and IL-1B (+3953) Gene Polymorphism in Syrian Patients with Aggressive Periodontitis.* *ISRN Dentistry.* 1-5
30. **Sorensen, LK. et al., 2009.** *Aggressive periodontitis and chronic arthritis: Blood mononuclear cell gene expression and plasma protein levels of cytokines and cytokine inhibitors* *Periodontol.* 80.2:282-9.
31. **Trevilatto.P.C, et al.2011.** *Association of IL1 gene polymorphisms with chronic periodontitis in Brazilians.* *Archives of Oral Biology* 5 6; 5 4 – 6 2.

32. **Tervonen, T., et al., 2007.** Polymorphisms in the CD14 and IL-6 genes associated with periodontal disease. *J Clin Periodontol.* 34. 5; 377-83.
33. **TorkZaban, P., et al., 2010.** Evaluation of Polymorphism of IL-10 in Children with Gingivitis. *J Mash Dent Sch;* 34.1: 7-14.
34. **Tabibzadeh, Z., et al., 2009.** Relationships between smoking & IL-1 β concentrations in chronic periodontal patients' .*Journal of Dental School Shahid Beheshti University of Medical Sciences.* 26.4:375-381.
35. **Viana. MB. et al., 2011.** Methylation pattern of IFN- γ and IL-10 genes in periodontal tissues. *Immunobiology* 21.6: 936– 941.
36. **Wagner, J., et al., 2007.** Prevalence of OPG and IL-1 gene polymorphisms in chronic periodontitis. *J Clin Periodontol;* 34.10: 823-7.

CORRESPONDING ADDRESS:

Dr. Jalaleddin, H. Hamissi

Associate Professor in Dental Caries Prevention Research Center and Department of Periodontics, Qazvin University Medical Sciences, Qazvin, Iran.

College of Dentistry

Qazvin University of Medical Science

Shaheed Bahonar Bly,

Qazvin, 34197-59811., I.R.Iran.

Contact:

Cell: ++989121812543

Email:

jhamissi@qums.ac.ir

jhamissi@gmail.com