

Current trends of genetics in apical periodontitis research

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Abstract: Genetics is an emerging topic in endodontic research focusing on the host response regarding the pathogenesis of apical periodontitis (AP). A number of genetic epidemiological studies carried out by many investigators worldwide have shown evidence of an association between certain candidate genes and AP. Some studies have been conducted on knockout mice with a deficiency in certain proteins, leading to more or less severe AP, and thus suggesting a pivotal role of these genes in AP pathogenesis. Other research has evaluated the association between genetic polymorphisms in humans with different AP aspects; these studies pointed out that genetic polymorphisms in some candidate genes are involved in inter-individual variations in their response to AP. Therefore, the objective of this report was to provide an updated overview of the genes involved in AP pathogenesis, with a focus on the most relevant candidate genes.

Keywords: Periapical Periodontitis; Polymorphisms, Genetic; Genes; Pathology; Endodontics.

Introduction

Apical periodontitis (AP) is generally a sequel of a root canal system infection.¹ Although the infection of the root canal system by pathogens is the main factor involved in its pathogenesis, AP is considered a multifactorial condition, in which other aspects also need to be taken into consideration. Host risk factors such as age, gender and systemic conditions have been evaluated by innumerable researchers for many years.^{2,3,4,5,6} However, the influence of the host's genetic background on AP pathogenesis is an emerging topic in endodontic research.

In fact, studies using knockout mice (KO) as an animal model,^{7,8,9,10,11,12,13,14,15} and studies with human samples,^{16,17,18,19,20,21,22,23,24,25,26,27,28,29} evaluating the complexity of endodontic biology, have revealed that many genes are involved in AP pathogenesis. These studies point to candidate genes that could act as genetic markers for inter-individual host response variations in AP establishment and formation.

So far, these studies have suggested the hypothesis that AP pathogenesis is a result of a complex interplay between microbial factors and genes. Therefore, the objective of this report was to provide an updated overview of the genes involved in AP pathogenesis, with a focus on the most relevant candidate genes.

Literature search strategy

This report systematically reviewed the current trends of genetics in AP pathogenesis research. Studies using KO and wild-type mice as the control, with experimentally induced AP, were included to enable identification of the candidate genes based on animal models. In contrast, only studies evaluating the association between genes (genetic polymorphisms) and AP phenotypes were considered in the task of identification the genes and genetic polymorphisms involved in AP pathogenesis in humans.

A systematic screening of the literature up to March 17, 2018, was undertaken using three electronic databases (PubMed, Scopus and Web of Science), including a hand search of corresponding reference lists and citation searching of key papers

without language or date restrictions. Grey literature was also consulted through OpenGrey (<http://www.opengrey.eu>). Researchers were contacted to identify additional studies. The MeSH (Medical Subject Headings) terms (www.nlm.nih.gov/mesh/meshhome.html), related terms, and free terms used in the search were “Apical Periodontitis,” “Periapical Periodontitis,” “Periapical Abscess,” “Polymorphism,” “Genetic,” “Polymorphism, Single Nucleotide,” and “Knockout.” The Boolean research strategy used is reported in Table 1.

Two authors (E.C.K. and L.A.A.) independently assessed selected titles and abstracts to validate the inclusion criteria. Studies appearing in more than one database were considered only once. In these cases, in which the abstract and the title were not clear, the study was read fully to minimize the possibility of overlooking important studies. The full text of

Table 1. Search strategy

| Search 1: Studies with animal models | |
|--|--|
| PubMed | #1 (Periapical Periodontitis [MeSH Terms]) OR Periapical Periodontitis [Title/Abstract] OR Periapical Abscess [MeSH Terms] OR Periapical Abscess [Title/Abstract] OR Apical Periodontitis [Title/Abstract] #2 (knockout[Title/Abstract]) #1 and #2 |
| WOS | #1 TOPIC: (“Periapical Periodontitis”) OR TOPIC: (“Periapical Abscess”) OR TOPIC: (“Apical Periodontitis”) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years #2 TOPIC: (knockout) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years #1 and #2 |
| Scopus | #1 (TITLE-ABS-KEY (“Periapical Periodontitis”) OR TITLE-ABS-KEY (“Periapical Abscess”) OR TITLE-ABS-KEY (“Apical Periodontitis”)) #2 TITLE-ABS-KEY (knockout) #1 and #2 |
| Search 2: Genetic polymorphism studies in humans | |
| PubMed | #1 (Periapical Periodontitis [MeSH Terms]) OR Periapical Periodontitis [Title/Abstract] OR Periapical Abscess [MeSH Terms] OR Periapical Abscess [Title/Abstract] OR Apical Periodontitis [Title/Abstract] #2 (Polymorphism, Genetic [MeSH Terms]) OR Polymorphism, Genetic [Title/Abstract] OR Polymorphism, Single Nucleotide [MeSH Terms] OR Polymorphism, Single Nucleotide [Title/Abstract] #1 and #2 |
| WOS | #1 TOPIC: (“Periapical Periodontitis”) OR TOPIC: (“Periapical Abscess”) OR TOPIC: (“Apical Periodontitis”) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years #2 TOPIC: (“Genetic Polymorphism”) OR TOPIC: (“Single Nucleotide Polymorphism”) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years #1 and #2 |
| Scopus | #1 (TITLE-ABS-KEY (“Periapical Periodontitis”) OR TITLE-ABS-KEY (“Periapical Abscess”) OR TITLE-ABS-KEY (“Apical Periodontitis”)) #2 (TITLE-ABS-KEY (“Genetic Polymorphism”) OR TITLE-ABS-KEY (“Single Nucleotide Polymorphism”)) #1 and #2 |

all potentially relevant studies was reviewed. Any disagreement was discussed and solved by consensus between the authors. Data from the included studies were extracted and organized into tables. Figure 1 presents a flowchart of the review process. Twelve studies with KO mice and 14 studies conducted on humans were identified.

Candidate genes involved in AP pathogenesis and phenotype, based on knockout animal studies

In endodontics, animal models—mainly of KO mice—have been a valuable tool to understand the role of genes in the progression of AP. A KO mouse is a genetically modified mouse (*Mus musculus*), in which researchers have inactivated, or “knocked out,” an existing gene. KO mice are a valuable tool for geneticists to understand the role of a gene in embryonic development, normal physiological homeostasis and pathological processes. Since humans and mice share about 99% of the same genes, this animal model is a good analogue for many human biological processes,³⁰ including AP pathogenesis. For geneticists, the targeted deletion of a gene in a mouse provides an important method to determine the biological role of a specific gene, and is useful in studying the *in vivo* gene function. It is also the best way to delineate the biological role of a protein.³¹ Our review included 12 articles that used KO mice as a model to study the role of a specific gene in AP formation and progression, as well as pathogenesis.

In these studies, an experimentally AP was induced in molars for different periods, and compared with AP formation and progression in wild-type mice. These studies are presented in Table 2, together with the description of candidate genes.

After AP induction, KO mice for *IL6*,⁷ *OPN*,⁸ *iNOS*,⁹ *TLR22*,¹⁰ *IL17RA*,¹¹ *MyD88*¹² and *MMP9*¹³ developed more severe AP than wild-type mice; on the other hand, KO mice for *IL22*³² and for *CB2*³³ developed less severe AP. Animals deficient in *PHOX*, which mediates the generation of reactive oxygen species, did not present alterations in the AP phenotype.⁹

These findings suggest that *IL6*, *IL17AR*, *OPN*, *iNOS*, *MMP9*, *TLR2* and *MyD88* are candidate genes, which might increase the risk for more severe AP phenotypes. On the other hand, *IL22* and *CB2* may be involved as candidate genes in protection from AP.

Studies evaluating genetic polymorphisms

In the past decade, a growing number of studies have demonstrated that genetic polymorphisms play an important role in AP pathogenesis and phenotype.^{16,17,18,19,20,21,22,23,24,25,26,27,28,29} The genetic polymorphisms studied in endodontics have so far focused on single nucleotide polymorphisms, also known as SNP. These genetic polymorphisms are the most common form of DNA sequence variation, and account for more than 90% of all variations present in the human genome.³⁴ Genetic polymorphisms could serve as useful genetic markers for identifying genes associated with the pathogenesis of complex alterations, such as AP.

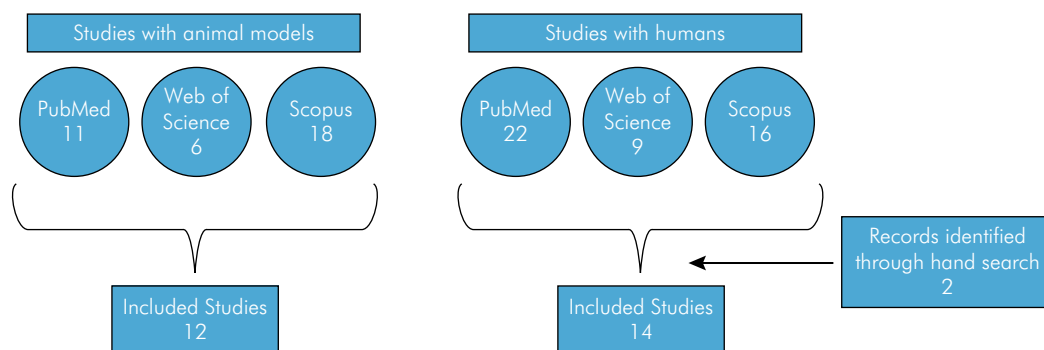


Figure 1. Flowchart of the review process.

Table 2. List of candidate genes, in alphabetic order, based on the animal knockout (KO) model studies.

| Gene official full name | Nomenclature | References | Gene/protein Function* |
|---|--------------|--|--|
| Cannabinoid Receptor 2 | CB2 | Nikolaeva et al. (2015) ³³ | The cannabinoid receptors are members of family 1 of the G-protein-coupled receptors and are located in immune cells. |
| Nitric Oxide Synthase | iNOS | Silva et al. (2011) ⁹ | The protein encoded by this gene belongs to the family of nitric oxide synthases, which synthesize nitric oxide. Nitric oxide is a reactive free radical that acts as a biologic mediator in several processes, including antimicrobial activities. |
| Interleukin 6 | IL6 | Huang et al. (2001) ⁷ | This gene encodes a cytokine that functions in inflammation and in the maturation of B cells. |
| Interleukin 22 | IL22 | Oliveira et al. (2015) ¹⁴ | This gene encodes a cytokine that contributes to the inflammatory response. is a α -helical cytokine that binds to a heterodimeric cell surface receptor composed of IL-10R2 and IL-22R1 subunits. |
| Interleukin 17 Receptor A | IL17RA | AlShwaimi et al. (2013) ¹¹ | is a proinflammatory cytokine secreted by activated T-lymphocytes. It is a potent inducer of the maturation of CD34-positive hematopoietic precursors into neutrophils. |
| Matrix Metalloproteinase 9 | MMP9 | Wan et al. (2014) ¹³ | is a protein-coding gene that plays an essential role in local proteolysis of the extracellular matrix, in leukocyte migration and in bone osteoclastic resorption. |
| Myeloid Differentiation Primary Response 88 | MyD88 | Silva et al. (2014) ¹² | This gene encodes a cytosolic adapter protein, which has a central role in the innate and adaptive immune response. acts as an essential signal transducer in the interleukin-1 and signaling pathways. |
| Osteopontin | OPN | Rittling et al. (2010) ⁸ | Osteopontin is an extracellular structural protein and an organic component of bone. It is involved in the regulation of immune responses and enhancement of leucocyte migration |
| Toll Like Receptor 2 | TLR2 | Silva et al. (2012); ¹⁰ Oliveira et al. (2015); ¹⁴ Rider et al. (2016); ¹⁵ Barreiros et al. (2018) | TLR2 and TLR4 are protein coding for genes that play a fundamental role in pathogen recognition and activation of innate immunity. They are single, membrane-spanning, non-catalytic receptors usually expressed on sentinel cells, such as macrophages and dendritic cells, which recognize structurally conserved molecules derived from microorganisms. |
| Toll Like Receptor 4 | TLR4 | Rider et al. (2016) ¹⁵ | |

Note: *<http://www.genecards.org/cgi-bin/carddisp.pl>. Only the genes resulting in less or more severe AP are presented here.

Genetic association studies have been conducted to evaluate the association between genetic polymorphisms and different AP phenotypes, and thus determine whether genetic polymorphisms are associated with AP. If there is in fact an association, then the specific allele, genotype or haplotype of a polymorphism is found more often than what is expected by chance in the affected group. Different study designs were used, such as a comparison of 1) acute AP and chronic AP; 2) persistent AP and a periapical healed periodontium; and 3) deep caries lesion with AP and deep caries lesion without AP.

Table 3 presents a list of these studies, together with the genes and polymorphisms evaluated, including the respective study design used. In fact, these studies have provided new etiologic perspectives for AP pathogenesis, with a greater focus on host response.

Final considerations and conclusions

The present review clearly highlights that genetic factors may contribute to inter-individual variation in AP pathogenesis and severity of host response (phenotype). It is important to emphasize that candidate genes were identified based on the observations and results obtained from the KO animal studies. If a deficiency of genes was involved in more or less severe AP, these genes became candidates to be studied in humans. However, it is also important to underscore that studies with animal models are not the only way to select candidate genes to be evaluated in human samples. The functions of the gene or the gene family in question are also important clues. Genes are considered candidate genes for AP pathogenesis, if genetic polymorphisms

Table 3. List of articles and genetic polymorphisms evaluated by the authors.

| Authors/year | Study design | Genes/ Polymorphisms | Results |
|---|---|--|---|
| Sá et al. (2007) ¹⁶ | 45 cases of symptomatic dental abscesses and 53 cases of asymptomatic inflammatory AP without previous exacerbation | CD14 (-260 C/T, rs2569190) IL1B (+3954 C/T, rs1143634) IL6 (-174 G/C, rs1800795) IL10 (-1082 G/A, rs1800896) TNFA (-308 G/A, rs1800629) | Genotype and allele distribution for the genetic polymorphism in IL6 was associated with symptomatic dental abscesses. |
| Siqueira Junior et al. (2009) ¹⁷ | 18 cases with PAP and 44 cases with root-canal-treated teeth exhibiting healthy/healing periradicular tissues | FcgRIIA (R131 or H131, rs1801274) FCgRIIB (NA1 or NA2, rs1050501) IL1A (-889, rs1800587) IL1B (+3954, rs1143634) | There was a statistical association observed for the genetic polymorphism in the FcγRIIb gene (p<0.001). |
| Morsani et al. (2011) ¹⁸ | 34 cases with signs/symptoms of AP and 61 controls showing healing periradicular tissues | IL1B (+3954, rs1143634) | There was an association between the genetic polymorphisms and AP (p<0.001). |
| Siqueira Junior et al. (2011) ¹⁹ | 26 cases with PAP and 43 cases with root-canal-treated teeth exhibiting healthy/healing periradicular tissues | FcgRIIIA (V/F158, rs396991) | The genetic polymorphism in FcγRIIIa was not associated with AP. |
| Menezes-Silva et al. (2012) ²⁰ | 158 cases with deep carious lesions but no periapical lesions, and 110 cases with periapical lesions and deep carious lesions | MMP2 (rs243865, rs2285053, rs243847, rs2287074, rs9923304, rs11639960) MMP3 (rs639752, rs650108, rs679620, rs522616) MMP9 (rs3918253, rs17576, rs17577) MMP13 (rs2252070) MMP14 (rs1042704) TIMP2 (rs9894526) | The genetic polymorphisms rs639752 (p=0.03) and rs679620 (p=0.004) in MMP3 were associated with AP. An altered transmission of MMP2 haplotypes (p=0.000004) was observed. |
| Salazar-Pelaéz et al. (2012) ²¹ | 27 cases with PAP and 27 cases with a healthy periapex | IL1A (-889, rs1800587) IL1B (+3954, rs1143634) | There was no association of the polymorphisms evaluated with AP (p>0.05). |
| Amaya et al. (2013) ²² | 63 cases with acute suppurative AP and 57 diagnosed with chronic nonsuppurative AP | IL1B (rs1143634) IL8/CXCL8 (rs4073) IL12B (rs3212227) TNFA (rs1800629) | An association was observed for the genetic polymorphism IL8/CXCL8 -251 (rs4073) (p=0.04). |
| Rôças et al. (2014) ²³ | 41 cases with post-treatment PAP and 42 cases with root-canal-treated teeth exhibiting healthy/healing periradicular tissues | CD14 (-260 C/T, rs2569190) TLR4 (+896A>G, rs4986790) | There was no association of the polymorphisms evaluated with AP (p>0.05). |
| Dill et al. (2015) ²⁵ | 136 cases with deep carious lesions and periapical lesions and 180 cases with deep carious lesions but no periapical lesions | IL10 (rs5743626) IL1B (rs1143643, rs1143634 and rs16062) TNF (rs1800629) IL6 (rs2069830) OPG (rs1131380) RANKL (rs12721445) RANK (rs35589394) | Genetic polymorphism in IL1B (rs1143643) showed allelic (p=0.02) and genotypic (p=0.004) association with AP. |
| Evrosimovska et al. (2015) ²⁴ | 120 cases with chronic AP and 120 cases without any signs of chronic or acute inflammatory process | MMP8 (-799 C/T) | MMP-8 polymorphism -799 C/T was a risk factor for expression of chronic AP (p<0.05). |
| Maheshwari et al. (2016) ²⁶ | 183 cases with deep carious lesions and AP, and 217 cases with deep carious lesions but without AP | HSPA4 (rs14355) HSPA6 (rs1042881) HSPA1L (rs2075800, rs2227956 and rs2227955) HSPA4L (rs1380154) HSPA9 (rs1042665, rs10117) | Genetic polymorphisms in HSPA1L and HSPA6 showed significant allelic association (p<0.05). We also observed altered transmission of HSPA1L haplotypes (p=0.03). |
| Trombone et al. (2016) ²⁷ | 111 patients presenting periapical granulomas, and 214 controls | MMP1 (-1607 1G/2G, rs1799750) | The MMP1-1607 1G/2G and 1G/2G+2G/2G genotypes were significantly more prevalent in AP patients than in the controls. |
| Miri-Moghaddam et al. (2017) ²⁸ | 50 cases with acute AP abscesses and 50 patients with asymptomatic AP | TLR4 (Thr399Ile / 1196 C>T, rs4986791 and Asp299Gly / +896 A>G, rs4986790) | The polymorphism Thr399Ile in TLR4 may play a role in the pathogenesis of acute apical abscesses. |
| Petean et al. (2018) ²⁹ | 64 cases with signs/symptoms of PAP and 84 subjects with root-canal-treated teeth exhibiting healthy periradicular tissues. | RANK (rs3826620), RANKL (rs9594738) OPG (rs2073618) | Genetic polymorphisms in RANK rs3826620 (p=0.02) and RANKL rs9594738 (p=0.03) were associated with PAP. |

Note: PAP means persistent apical periodontitis.

can be identified and associated with the condition. There may be one or many candidate genes in each gene family. In addition, a genome-wide association study approach, which uses a high density of genetic markers spread over the entire human genome and a large sample size, could identify potentially new genetic polymorphisms.

Another important aspect observed from this review was the lack of validation studies. Only few researchers have evaluated whether genetic polymorphisms in genes involved in AP pathogenesis in animal models are also involved in AP phenotypes in humans. Furthermore, this review identified the absence of proper replication of genetic association studies in different populations. Although replications are considered a key part of genetic epidemiological research, only few research groups aimed to replicate previous studies with results compiled in two meta-

analyses,^{35,36} which report an association between the genetic polymorphism – 308 G>A in *TNF-α* with acute AP and the polymorphism +3954 C>T in *IL1B* with persistent AP.

In summary, in the present review, we have systematically collected and screened various studies exploring the role of genes and genetic polymorphisms in AP pathogenesis, thus presenting an updated overview of the field and offering useful information for carrying out future research focusing on the role of various genetic factors. Based on the available data, further identification of candidate genes and their role in AP pathogenesis and phenotype was deemed warranted and necessary.

Moreover, patients with AP may have one or more genetic polymorphisms in several different genes, requiring the translation of new genetic findings into meaningful dental practice or public health applications.

References

- Nair PN. Pathogenesis of apical periodontitis and the causes of endodontic failures. *Crit Rev Oral Biol Med*. 2004 Nov;15(6):348-81. <https://doi.org/10.1177/154411130401500604>
- López-López J, Jané-Salas E, Martín-González J, Castellanos-Cosano L, Llamas-Carreras JM, Velasco-Ortega E et al. Tobacco smoking and radiographic periapical status: a retrospective case-control study. *J Endod*. 2012;38(5):584-8. <https://doi.org/10.1016/j.joen.2012.02.011>
- Aminoshariae A, Kulild JC. Association of Functional Gene Polymorphism with Apical Periodontitis. *J Endod*. 2015 Jul;41(7):999-1007. <https://doi.org/10.1016/j.joen.2015.03.007>
- Hussein FE, Liew AK, Ramlee RA, Abdullah D, Chong BS. Factors associated with apical periodontitis: a multilevel analysis. *J Endod*. 2016 Oct;42(10):1441-5. <https://doi.org/10.1016/j.joen.2016.07.009>
- Khalighinejad N, Aminoshariae MR, Aminoshariae A, Kulild JC, Mickel A, Fouad AF. Association between systemic diseases and apical periodontitis. *J Endod*. 2016 Oct;42(10):1427-34. <https://doi.org/10.1016/j.joen.2016.07.007>
- Vengerfeldt V, Mändar R, Nguyen MS, Saukas S, Saag M. Apical periodontitis in southern Estonian population: prevalence and associations with quality of root canal fillings and coronal restorations. *BMC Oral Health*. 2017 Dec;17(1):147. <https://doi.org/10.1186/s12903-017-0429-7>
- Huang GT, Do M, Wingard M, Park JS, Chugal N. Effect of interleukin-6 deficiency on the formation of periapical lesions after pulp exposure in mice. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001 Jul;92(1):83-8. <https://doi.org/10.1067/moe.2001.115025>
- Rittling SR, Zetterberg C, Yagiz K, Skinner S, Suzuki N, Fujimura A, et al. Protective role of osteopontin in endodontic infection. *Immunology*. 2010 Jan;129(1):105-14. <https://doi.org/10.1111/j.1365-2567.2009.03159.x>
- Silva MJ, Sousa LM, Lara VP, Cardoso FP, Carmo Júnior GM, Totola AH, et al. The role of iNOS and PHOX in periapical bone resorption. *J Dent Res*. 2011 Apr;90(4):495-500. <https://doi.org/10.1177/0022034510391792>
- Silva RA, Ferreira PD, De Rossi A, Nelson-Filho P, Silva LA. Toll-like receptor 2 knockout mice showed increased periapical lesion size and osteoclast number. *J Endod*. 2012 Jun;38(6):803-13. <https://doi.org/10.1016/j.joen.2012.03.017>
- AlShwaimi E, Berggreen E, Furusho H, Rossall JC, Dobeck J, Yoganathan S et al. IL-17 receptor A signaling is protective in infection-stimulated periapical bone destruction. *J Immunol*. 2013 Aug;191(4):1785-91. <https://doi.org/10.4049/jimmunol.1202194>
- Silva RAB, Nelson-Filho P, Lucisano MP, De Rossi A, Queiroz AM, Silva LAB. MyD88 knockout mice develop initial enlarged periapical lesions with increased numbers of neutrophils. *Int Endod J*. 2014 Jul;47(7):675-86. <https://doi.org/10.1111/iej.12204>

13. Wan C, Yuan G, Yang J, Sun Q, Zhang L, Zhang J et al. MMP9 deficiency increased the size of experimentally induced apical periodontitis. *J Endod.* 2014 May;40(5):658-64. <https://doi.org/10.1016/j.joen.2014.01.003>
14. Oliveira KM, Silva RA, De Rossi A, Fukada SY, Feres M, Nelson-Filho P et al. Absence of interleukin 22 affects the oral microbiota and the progression of induced periapical lesions in murine teeth. *Int Endod J.* 2015 Jan;48(1):46-59. <https://doi.org/10.1111/iej.12274>
15. Rider D, Furusho H, Xu S, Trachtenberg AJ, Kuo WP, Hirai K et al. Elevated CD14 (Cluster of Differentiation 14) and Toll-Like Receptor (TLR) 4 Signaling Deteriorate Periapical Inflammation in TLR2 Deficient Mice. *Anat Rec (Hoboken).* 2016 Sep;299(9):1281-92. <https://doi.org/10.1002/ar.23383>
16. Sá AR, Moreira PR, Xavier GM, Sampaio I, Kalapothakis E, Dutra WO et al. Association of CD14, IL1B, IL6, IL10 and TNFA functional gene polymorphisms with symptomatic dental abscesses. *Int Endod J.* 2007;40(7):563-72. <https://doi.org/10.1111/j.1365-2591.2007.01272.x>
17. Siqueira JF Jr, Rôças IN, Provenzano JC, Daibert FK, Silva MG, Lima KC. Relationship between Fcγ3 receptor and interleukin-1 gene polymorphisms and post-treatment apical periodontitis. *J Endod.* 2009 Sep;35(9):1186-92. <https://doi.org/10.1016/j.joen.2009.05.006>
18. Morsani JM, Aminoshariae A, Han YW, Montagnese TA, Mickel A. Genetic predisposition to persistent apical periodontitis. *J Endod.* 2011 Apr;37(4):455-9. <https://doi.org/10.1016/j.joen.2011.01.009>
19. Siqueira Junior JF, Rôças IN, Provenzano JC, Guilherme BP. Polymorphism of the FcγRIIIa gene and post-treatment apical periodontitis. *J Endod.* 2011 Oct;37(10):1345-8. <https://doi.org/10.1016/j.joen.2011.06.025>
20. Menezes-Silva R, Khaliq S, Deeley K, Letra A, Vieira AR. Genetic susceptibility to periapical disease: conditional contribution of MMP2 and MMP3 genes to the development of periapical lesions and healing response. *J Endod.* 2012 May;38(5):604-7. <https://doi.org/10.1016/j.joen.2012.02.009>
21. Salazar-Pelaéz LM, Fernández Grisales RO, Zulúaga Yepes OE, Vargas KO, Tobón Calle D. IL-1 gene polymorphisms and the risk of chronic periapical periodontitis in a population from Antioquia, Colombia. *Arch Oral Biol.* 2012;8(1):19-30.
22. Amaya MP, Criado L, Blanco B, Gómez M, Torres O, Flórez L et al. Polymorphisms of pro-inflammatory cytokine genes and the risk for acute suppurative or chronic nonsuppurative apical periodontitis in a Colombian population. *Int Endod J.* 2013 Jan;46(1):71-8. <https://doi.org/10.1111/j.1365-2591.2012.02097.x>
23. Rôças IN, Siqueira JF Jr, Del Aguila CA, Provenzano JC, Guilherme BP, Gonçalves LS. Polymorphism of the CD14 and TLR4 genes and post-treatment apical periodontitis. *J Endod.* 2014 Feb;40(2):168-72. <https://doi.org/10.1016/j.joen.2013.10.006>
24. Evrosimovska B, Dimova C, Popovska L, Zabokova-Bilbilova E. Matrix metalloproteinase-8 gene polymorphism in chronic periapical lesions. *Prilozi.* 2015;36(2):217-224. <https://doi.org/10.1515/prilozi-2015-0070>
25. Dill A, Letra A, Souza LC, Yadlapati M, Bigueti CC, Garlet GP et al. Analysis of multiple cytokine polymorphisms in individuals with untreated deep carious lesions reveals IL1B (rs1143643) as a susceptibility factor for periapical lesion development. *J Endod.* 2015 Feb;41(2):197-200. <https://doi.org/10.1016/j.joen.2014.10.016>
26. Maheshwari K, Silva RM, Guajardo-Morales L, Garlet GP, Vieira AR, Letra A. Heat Shock 70 Protein Genes and Genetic Susceptibility to Apical Periodontitis. *J Endod.* 2016 Oct;42(10):1467-71. <https://doi.org/10.1016/j.joen.2016.07.010>
27. Trombone AP, Cavalla F, Silveira EM, Andreo CB, Francisconi CF, Fonseca AC et al. MMP1-1607 polymorphism increases the risk for periapical lesion development through the upregulation MMP-1 expression in association with pro-inflammatory milieu elements. *J Appl Oral Sci.* 2016 Jul-Aug;24(4):366-75. <https://doi.org/10.1590/1678-775220160112>
28. Miri-Moghaddam E, Farhad-Mollashahi N, Baghaee E, Bazi A, Garma Y. Role of Thr399Ile and Asp299Gly polymorphisms of toll-like receptor-4 gene in acute dental abscess. *J Clin Exp Dent.* 2017 Feb;9(2):e196-201.
29. Mazzi-Chaves JF, Petean IBF, Soares IMV, Salles AG, Antunes LAA, Segato RAB et al. Influence of genetic polymorphisms in genes of bone remodeling and angiogenesis process in the apical periodontitis. *Braz Dent J.* 2018 Mar-Apr;29(2):179-83. <https://doi.org/10.1590/0103-6440201802260>
30. Capecchi MR. Targeted gene replacement. *Sci Am.* 1994 Mar;270(3):52-9. <https://doi.org/10.1038/scientificamerican0394-52>
31. Hall B, Limaye A, Kulkarni AB. Overview: generation of gene knockout mice. *Curr Protoc Cell Biol.* 2009 Sep;44(1). <https://doi.org/10.1002/0471143030.cb1912s44>
32. Oliveira KM, Nelson-Filho P, Silva LA, Küchler EC, Gatón-Hernandez P, Silva RA. Three-dimensional micro-computed tomography analyses of induced periapical lesions in transgenic mice. *Ultrastruct Pathol.* 2015;39(6):402-7. <https://doi.org/10.3109/01913123.2015.1060283>
33. Nikolaeva EP, Cox TC, Flake NM. Osseous characteristics of mice lacking cannabinoid receptor 2 after pulp exposure. *J Endod.* 2015 Jun;41(6):853-7. <https://doi.org/10.1016/j.joen.2015.01.030>
34. Pramanik S, Saha D. The genetic influence in fluorosis. *Environ Toxicol Pharmacol.* 2017 Dec;56:157-62. <https://doi.org/10.1016/j.etap.2017.09.008>
35. Salles AG, Antunes LA, Carvalho PA, Küchler EC, Antunes LS. Association between apical periodontitis and TNF-α -308 G>a gene polymorphism: a systematic review and meta-analysis. *Braz Dent J.* 2017 Sep-Oct;28(5):535-42. <https://doi.org/10.1590/0103-6440201701491>
36. Salles AG, Antunes LA, Küchler EC, Antunes LS. Association between apical periodontitis and interleukin gene polymorphisms: a systematic review and meta-analysis. *J Endod.* 2018 Mar;44(3):355-62. <https://doi.org/10.1016/j.joen.2017.11.001>