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Human Genetic Variations Associated with Periodontitis- A Mini Review

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Abstract: Periodontitis (PD) is a complex, multifactorial disease which involves participation of microbial and host factors. Microbes activate inflammatory response in the host which stimulates the periodontal cells to secrete metalloproteinases and other proteolytic enzymes eventually resulting in the tissue destruction and bone resorption. Numerous experimental reports have gathered information related to the potential biomarkers involved in PD. Genetic component of the host as well as the microorganism has been shown to play a pivotal role in the pathogenesis of the disease. Human genetic variation is considered to be a susceptibility factor in relation to PD. These variations could make an individual resistant or susceptible to infections caused by the microorganisms. Also, other factors such as food habits, lifestyle, smoking, alcoholism and poor oral hygiene practice can aggravate the disease. The magnitude of the disease PD that a patient develops is due to factors related to the individual's response to the bacterial colonization. Several inflammatory markers and the genes encoded by them are discussed in the present review. Thus the review provides a general overview of the genes and their proteins in association with different forms of PD.

Keywords: aggressive; chronic; genes; periodontitis; polymorphism.

INTRODUCTION

Periodontal disease (PD) is a complex disease with a complex interplay between host and microbial factors (Ashwin et al., 2015). PD is one of the most common diseases prevalent world-wide, characterized by the inflammation of gingiva and severe resorption of alveolar bones (Buduneli, 2012). Although the incidence of the disease is common, the World Health Organization (WHO) has reported it to a preventable disease. PD may also indicate a chronic inflammatory reaction happening in the host, which might be responsible for host cell destruction leading to other disorders (Lu et al., 2020). PD initiates as gum infection which progresses into the vicinity thereby damaging the soft tissue. Early treatment such as scaling and removal of plaque and tartar could avoid the loss of tooth due to bone resorption. There are two major forms of periodontal disease, which are: chronic and aggressive periodontitis. Aggressive periodontitis (AP) is characterized by a rapid and early onset of the disease eventually leading to destruction of the ligaments of periodontium and resorption of alveolar bones in healthy individuals. While chronic periodontitis (CP) is due to accumulation of dental plaque and tartar leading to chronic inflammation of tissues of the periodontium. Family history is suggestive of genetic traits in aggressive periodontitis. CP is an infectious disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment and bone loss, (Marickar, Geetha and Neelakantan, 2014; Panda et al., 2014)(Silva et al., 2020).

The most common form of PD is which is more prevalent in adults, with a few cases recorded in children. The magnitude of tissue destruction is consistent with subgingival calculus, variable microbial pattern and possibly influenced by and or associated with systemic diseases (Shahana and Muralidharan, 2016)(Marickar, Geetha and Neelakantan, 2014)(Shahana and Muralidharan, 2016)(Marickar, Geetha and Neelakantan, 2014). The major signs and symptoms of PD include swollen and bleeding gums, halitosis, pus between teeth and gums, painful chewing and a change in the way teeth fit together during a bite. In addition to the genetic predisposition, factors which can increase risk of PD are gingivitis, poor oral health hygiene, smoking or chewing tobacco, certain medication, inadequate nutrition and conditions that cause decreased immunity. PD is

initiated by microorganisms forming a biofilm which is more often refractory to treatment. The microbial pathogens in the subgingival biofilm is further affected by lifestyle factors such as smoking, stress, diet and environment. PD can also be influenced by acquired diseases which reduce or hamper an optimal host response. Apart from these factors variations in the crucial genes might be responsible for susceptibility to PD. Aggressive periodontitis is inherited as Mendelian traits and serves as excellent models to identify genetic factors associated with periodontitis. However, other genetic risk factors i.e. complex gene interactions, gene - environmental and gene - lifestyle interactions also contribute to the disease phenotype (Sanz et al., 2020). The goal of this review was to identify potential genes associated with host, microbial factors and variations influencing PD development ((Ashwin and Muralidharan, 2015); (Girija et al., 2019). Our department is passionate about research we have published numerous high quality articles in this domain over the past years ((Kavitha et al., 2014) , (Praveen et al., 2001),(Devi and Gnanavel, 2014), (Putchala et al., 2013), (Vijayakumar et al., 2010), (Lekha et al., 2014a, 2014b) (Danda, 2010) (Danda, 2010) (Parthasarathy et al., 2016) (Gopalakannan, Senthilvelan and Ranganathan, 2012), (Rajendran et al., 2019), (Govindaraju, Neelakantan and Gutmann, 2017), (P. Neelakantan et al., 2015), (PradeepKumar et al., 2016), (Sajan et al., 2011), (Lekha et al., 2014a), (Neelakantan, Grotra and Sharma, 2013), (Patil et al., 2017), (Jeevanandan and Govindaraju, 2018), (Abdul Wahab et al., 2017), (Eapen, Baig and Avinash, 2017), (Menon et al., 2018), (Wahab et al., 2018), (Vishnu Prasad et al., 2018), (Uthrakumar et al., 2010), (Ashok, Ajith and Sivanesan, 2017), (Prasanna Neelakantan et al., 2015).

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Genetic variations in the form of mutations and polymorphisms have been identified so as to define the genetic basis of PD in syndromic conditions. For example, in Papillon – Lefevre syndrome, which follows an autosomal recessive pattern of inheritance, presents with an early onset of periodontitis, which was attributed to the loss of function mutations in the cathepsin-C gene (Hewitt et al., 2004). Another study reports the association of mutations in lysosomal trafficking regulator gene (LYST) in Chediak – Higashi syndrome which was characterised by AP (Thumbigere et al., 2018). The disorder leukocyte adhesion deficiency type I, an autosomal recessive disorder is caused by mutations in CD18 (beta 2 integrin) was associated with AP (Bashir et al., 2018). Microbial factors would also contribute to PD (Sohaib Shahzan, Smiline Girija and Vijayashree Priyadharsini, 2019). The subgingival population of microbial biofilm including the red complex pathogens such as Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia and Aggregatibacter antinomycetemcomitans which triggers innate and adaptive immune response (Silva et al., 2015). The association of periodontal illness with rare syndromic conditions following a Medelian trait demonstrates the involvement of genetic factors in the etiology of PD. However, these rare forms of genetic diseases with a low prevalence rate do not always define the most common forms of periodontitis. Since PD is a complex disorder, cumulative effects of variants in different genes have to be studied to derive an association (Thamaraiselvan et al., 2015; Ushanthika et al., 2019)(Wang et al., 2020)(Thamaraiselvan et al., 2015; Ushanthika et al., 2019). Other factors, such as environmental and microbial agents also modify PD risk and expression of inflammatory markers (Girija et al., 2018; (Girija et al., 2020).

Research on new methods for investigation of disease condition at molecular level put the light of study interaction between host and parasite. The research in periodontal disease has been done based on vital molecular markers interleukin-1, interleukin-4, interleukin-6, and tumor necrosis factor alpha, vitamin D receptor and matrix metalloproteinase (Chrzęszczyk, no date; 'PR080: Thr399Ile polymorphism in chronic and aggressive periodontitis', 2018). Studies have analysed IL-1 genetic association with periodontitis in clinical practice. Many of them have returned a significant association between the IL-1 gene and the severity of periodontitis (Chrzęszczyk, Baczyńska and Konopka, 2014)(Gajendran, Parthasarathy and Tadepalli, 2018; Girija As and Priyadharsini J, 2019). In addition, IL-1 genotypes along with smoking habits were represented as a dangerous combination in case of PD (Sohaib Shahzan, Smiline Girija and Vijayashree Priyadharsini, 2019); (da Silva et al., 2020).

Common Genes Involved In Pd

TLR4

The toll like receptors 4 [TLR4] is mainly involved in the intracellular signaling process. It has been implicated in innate immune response to periodontopathogenic bacteria (Chrzęszczyk, Baczyńska and Konopka, 2014). A recent meta-analysis by Jin et al., identified variants which can render an individual susceptible for PD. The analysis included 8 studies, with 2453 control subjects and 2987 patients with CP and 462 patients with AP. The results demonstrated the association of TLR4C>G (rs7873784) allele in CP with Asian population, which is inherited in a recessive manner (Jin et al., 2016).

IL-13

Interleukin 13 (IL-13) gene encodes a 132-amino acid residue protein eliciting multiple biological functions. The type II T helper lymphocytes secrete IL-13 and other cytokines which inturn activate B cell humoral immunity leading to the process of inflammation. Earlier studies have reported a significant rise in the IL-13 levels during PD as a defense mechanism against pathogens expressing lipopolysaccharides. Hence, a comprehensive research on inflammatory mediators with a special emphasis on interleukins would unravel the pathways involved directly or indirectly in the etiopathogenesis of PD (Zhang et al., 2018).

IL-1

Polymorphisms of the interleukin encoded genes are the most widely studied variations related to PD. Interleukins are known to participate in processes which are required to initiate and maintain inflammatory responses. The expression of IL-1, facilitates the migration of leukocytes, production of inflammatory mediators, activation of B and T cells, stimulation of osteoblasts resulting in bone resorption and triggering apoptosis in cells. Since the level of expression and function of IL-1 produced in response to microbes contributes greatly to the susceptibility of periodontitis progression, polymorphisms of IL-1 encoding genes

could be considered to be susceptibility markers of PD (Inchingolo et al., 2020). A meta-analysis conducted by Feng and Liu identified the promoter polymorphism (-889C/T) of IL-1A gene to be associated with susceptibility to chronic periodontitis in African, European and American populations (Feng and Liu, 2020).
A study conducted by Puri et al, to evaluate the possible association between IL-1alpha(-889) polymorphism in Indian patients with AP and CP when compared to controls returned a significant association between the disease phenotype and genotypes. Homozygous genotype was more prevalent in AP whereas heterozygous genotype was common in CP cases (Puri et al., 2015).

IFN gamma

The cytokines play an important role in the defense process against microbial infections. A study conducted by employing (CA)n microsatellite marker in the interferon gamma receptor 1 (IFNGR1) gene polymorphism to assess the association with PD (Fraser et al., 2003). Although the study did not identify the contribution of IFNGR1 polymorphism, a combination of genotype with environmental factors and smoking produced a significant association, thus supporting the multi-gene - environmental model to demonstrate the susceptibility to PD.

Fc gamma receptor

The FcγRs (Fc gamma receptors) are placed on the cell-surface which acts as receptors for the Fc region of immunoglobulin G type of antibodies. They are known to induce phagocytosis, antibody-dependent cell cytotoxicity, activation of neutrophils and inhibition of B-cell activation by immune complexes. Thus, the FcγRs serve to link humoral and cell mediated immune responses triggered against periodontopathic bacteria. Interestingly, the genotype CC and the allele C of the polymorphic marker rs445509 of FCGR3A conferred protection against PD (Chai, no date).

Vitamin D Receptor

The bone mineral density, turnover in bones and diseases related to bone resorption have been associated with genetic polymorphism in the vitamin D receptor gene. The alveolar bone loss is a key feature in PD. The 3' untranslated region of the VDR gene includes a cluster of linked polymorphism: Bsml, Apal, Taql sites (Tobón-Arroyave, 2017; Murthykumar, Arjunkumar and Jayaseelan, 2019). Vitamin D receptor (VDR) gene polymorphism greatly influences the level or function of the vitamin D receptor. These polymorphisms have been implicated in the pathogenesis of periodontal and systemic disease which affect the bone tissue (Murthykumar, Arjunkumar and Jayaseelan, 2019).

Clinical Importance of Genetic Information in Diagnosis and Treatment

Clinicians and researchers have an important role to play in accumulating knowledge about the disease, its pattern of inheritance and to associate them with the likelihood of disease initiation before it occurs ((Smiline, Vijayashree and Paramasivam, 2018); (Girija As, Priyadharsini J and A, 2019). In case of aggressive periodontitis, genetic counselling will aid in providing advice and awareness to individuals regarding the maintenance of proper oral hygiene and dental health. Reducing inflammation with the help of natural compounds may not pose the risk of the development of antimicrobial resistant strains (Afreen et al., 2019). Prediction of susceptible members for AP can be identified and treatment can be started promptly (Kurt-Bayrakdar, Ozturk and Kara, 2020). Periodontitis is generally associated with other comorbid conditions or syndromic cases which can be diagnosed on the basis of clinical finding, genetic counselling and investigation such as karyotyping and polymerase chain reaction (Chai, Song and Leung, 2012)0; (Paramasivam, Priyadharsini and Raghunandhakumar, 2020). Once identified, educating patients, motivating them for regular check up and proper follow up after surgical and non surgical treatment can be advised (Ravi et al., 2017; Gajendran, Parthasarathy and Tadepalli, 2018).

CONCLUSION

Tremendous efforts have been taken by the clinicians to provide information regarding the genetic factors associated with different types of PD. Despite the fact that genome wide association studies and exposure based analysis have provided substantial evidence on the causative gene polymorphisms of periodontitis and their pathophysiological effect, the results remain controversial in different populations. Association studies have limited power to detect the rare genetic factors. Knowledge of the hereditary influence of disease is not a new finding and it seems that the oral cavity is not excluded from genetic factors. An amalgamation of clinical and knowledge on genetic factors can be considered as the best strategy towards the treatment options for PD. An exhaustive research on the variations in human genome, the epigenetic and environmental factors related to the disease phenotype could provide novel avenues towards designing better and more efficacious treatment modalities for the patients suffering from periodontitis.

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Conflict of Interest

None

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