

**FINAL REPORT**

**Sample, Report**

Date Of Birth: 09/20/1980  
Gender: Female

**Ordering Provider (13000007)**

Ronald McGlennen MD  
1410 Museum Campus Dr  
Chicago, IL 60606  
123-123-1234

**Sample Information**

Specimen#: 3033031027  
Accession#: 201702-09869  
Specimen: Oral Rinse(P)

Collected: 02/11/2017  
Received: 02/12/2017 12:57  
Reported: 02/15/2017 11:31

**Reason for Testing:** Patient assessment/post treatment, Diabetes, Cardiovascular disease

**CELSUS ONE: GENETIC ANALYSIS FOR MARKERS OF ORAL AND SYSTEMIC INFLAMMATION**

Type of Immunity	Gene Marker	Genotype	Inflammation Index
Innate	Beta-defensin 1 (DEFB1)	G/A	Low Risk
	CD14 (CD14)	T/T	
	Toll-like receptor 4 (TLR4)	AA/CC	
Acquired	Tumor necrosis factor alpha (TNF-alpha)	C/C	Intermediate Risk
	Interleukin 1 (IL1)	TT/CT	
	Interleukin 6 (IL6)	C/C	
	Interleukin 17A (IL17A)	G/G	
	Matrix Metalloproteinase 3 (MMP3)	5A/5A	

**Interpretation:**

The genotypes for markers DEFB1, CD14 and TLR4 for this individual collectively predict a normal phenotype for the innate immune system and a low risk for chronic systemic inflammation. Specifically, the expected level of gene expression, and or levels of these proteins, is normal in response to environmental and disease causing bacteria and other effectors of inflammation. See comment.

The genotypes for markers TNF-alpha, IL1, IL6, IL17A, and MMP3 predict a slightly enhanced immune response to specific pathogens and an intermediate risk for chronic systemic inflammation. Based on this, gene expression and the corresponding protein levels, in response to disease causing bacteria and the other effectors of the acquired immune system, are predicted to be increased. See comment.

**Disclaimer:** The reported genotypes are a subset of the group of genes that comprise the complete immune system. This genetic analysis may not detect specific immunologic diseases or predict the health and effectiveness of a person's immunity for specific diseases. Such an evaluation may require genetic counseling and testing directed to characterize those genetic conditions.

**Comments:**

The innate immune system is the body's first line of defense against pathogenic organisms and a major cause of oral and systemic inflammation. The innate immunity functions to create a physical and chemical barrier to bacteria, the recruitment of inflammatory cells to the site of infection, the release of cytokines and the activation of the complement cascade to localize and eliminate bacteria and recruit antigen-recognizing lymphocytes. The acquired immune system involves the production of specialized cells that eliminate or prevent pathogen growth and is the basis for immunologic memory.

- **Periodontitis:** The genotype for the innate immune system marker, DEFB1, predicts an inability to maintain a balance of commensal oral bacteria. Thus, there is a predisposition to periodontal pathogenic bacterial infection. The acquired immune system IL1 and MMP3 genotypes predict an accentuated inflammatory response to pathogenic periodontal bacteria. The cytokine IL1 acts in concert with TNF-alpha to stimulate bone resorption by osteoclasts and to promote the release of matrix metalloproteinases. Further, the presence of a 'T' allele in both the IL1 alpha and beta polymorphic loci is associated with an increased severity of chronic periodontitis. Individuals with the MMP3 5A/5A genotype have elevated levels of gene transcription and an increased local expression of MMP3, and are 3 times more likely to develop chronic periodontitis.
- **Cardiovascular:** Chronic inflammation is implicated in the etiology of cardiovascular disease (CVD). There is also strong evidence to support that polymorphisms within the promoter regions of the cytokine genes for IL1, IL6 and MMP3 are linked to levels of gene expression which are associated with chronic inflammation. The cytokine IL1 beta upregulates the recruitment of inflammatory cells and the levels of matrix metalloproteinase to the site of cholesterol deposition at sites of atherosclerosis. Matrix metalloproteinases function to remove extracellular matrix products which is considered a risk factor to destabilize arterial plaque. Specifically, the 5A/5A genotype is associated with a higher risk of myocardial infarction (MI) at young age (males < 60 years) which increases to a 10-fold risk in those who smoke.
- **Type II Diabetes:** The 'T' allele of the IL1 beta gene is correlated with elevated serum glucose and altered glucose homeostasis. Further, it has been shown that insulin producing beta cells in the pancreas in persons with type 2 diabetes mellitus (T2DM) also have increased levels of the cytokine IL1 beta. Consequently, clinical studies conclude that the IL1 SNPs are associated with development of diabetic nephropathy through interactions with other pro- and anti-inflammatory mediators.

Gene Marker	Nucleic Acid Assignment	Reference Sequence Number (rs)	Overview
Beta-defensin 1 (DEFB1)	3 prime variant G>A	rs1047031	Defensins have been identified to be produced as an immediate response to pathogenic bacteria lipopolysaccharides (LPS) and are important elements of the innate immune system. These proteins have broad-spectrum antimicrobial activity against bacteria, fungi and some viruses. The G>A (guanine to adenine) nucleotide base variant in the three-prime untranslated region of this gene has been shown to be associated with increased risk for both chronic and aggressive periodontitis. (1)
CD14	-260 C>T	rs2569190	CD14 is a receptor present on monocytes, macrophages, neutrophils and some B cells, and dendritic cells that recognizes bacterial cell wall lipopolysaccharides (LPS). Thus, it can stimulate the innate immune response via tumor necrosis factor alpha (TNF-alpha) production. Individuals possessing the C/C genotype at position -260 have been reported to have a two-fold increased susceptibility to periodontitis. Conversely, the T/T genotype has been identified in a significantly higher frequency in healthy individuals. The T/T genotype has also been associated with a decreased prevalence of Prevotella intermedia. (2)
Tumor necrosis factor alpha (TNF-alpha)	-857 C>T	rs1799724	Tumor necrosis factor-alpha (TNF-alpha) is a type of messenger protein, that is produced by white blood cells. TNF-alpha helps regulate the immune response through promotion of inflammation and prompts the production of other cells involved in the inflammatory response. TNF-alpha cytokine production in -857 T allele carriers tends to be elevated, and the incidence of the variant allele is reported to be significantly higher in periodontitis patients than in healthy subjects. (3)
Toll-like Receptor 4 (TLR4)	+896 A>G +1196 C>T	rs4986790 rs4986791	Toll-like receptors (TLRs) are signal molecules essential for the cellular response to bacterial cell wall lipopolysaccharides (LPS) and are viewed as important connector elements between the innate and acquired immune responses. TLR4 cytokine expression has been shown to be increased in both macrophages and gingival fibroblasts located in inflamed gingival tissues indicating its importance in the inflammatory process. Studies have shown that two TLR 4 variants, 896 A>G and 1196 C>T are frequently inherited together and individuals who inherit a composite genotype that contains the 896 G allele are hyporesponsive to LPS stimulation. (4)
Interleukin 1 (IL1)	-889 C>T +3954 C>T	rs1800587 rs1143634	Interleukin 1 (IL1) cytokines induce other immune cells to secrete matrix metalloproteins (MMPs) and prostaglandins that enhance the inflammatory processes in periodontal tissues. Additionally, IL1 is a strong stimulator of connective tissue degradation. The IL1 alpha -889 single nucleotide polymorphism (SNP) has been identified to be in complete linkage with the IL1 alpha +4845 SNP which has previously been reported in combination with the IL1 beta +3954 C>T SNP. Multiple studies have reported that the presence of a T allele in each of the IL1 alpha and IL1 beta genotypes are associated with periodontal disease severity. (5,6,7)
Interleukin 6 (IL6)	-174 C>G	rs1800795	The interleukin-6 (IL6) cytokine is involved in a wide variety of biological functions. It is produced in response to inflammatory stimuli such and tumor necrosis factor (TNF-alpha), interleukin 1, and bacterial and viral infection. IL6 is a regulator of B-cell responses, is a stimulator of osteoclast differentiation and bone resorption and is an inhibitor of bone formation. It has also been shown that carriers of a single G allele are more predisposed to periodontitis than C/C carriers and individuals carrying the G/G genotype have a further increased risk of periodontitis. (8)
Interleukin 17A (IL17A)	-197 G>A	rs2275913	IL17 consists of a group of cytokines produced by activated T-lymphocytes as an element of the acquired (secondary) immune response. IL17A, a specific IL17 cytokine, appears to have a strong feedback effect on regulation and enhancement of the innate (initial) immune response through recruitment of neutrophils and macrophages that secrete TNF-alpha and IL1 beta. IL17A G/A and A/A genotypes are reported to be present in higher frequencies in patients with periodontitis than the G/G genotype. The A allele of IL17A has also been associated with more severe clinical parameters such as probing depth, clinical attachment loss and enhanced gingival tissue inflammation. (9)
Matrix Metalloproteinase 3 (MMP3)	-1171 5A/6A	rs3025058	Matrix metalloproteinase (MMPs) comprise the most important pathway to tissue destruction resulting from periodontal disease. The primary function of MMPs is the pathological breakdown of extracellular matrix, most importantly collagen type I, which is found in the periodontal ligament and alveolar bone organic matrix. Studies report that individuals with the 5A/5A genotype are approximately two- to three-fold more likely to develop periodontitis than individuals with 5A/6A or 6A/6A genotypes. (10)

**References:**

1. Schaefer A, et al. The 3' UTR transition within DEFB1 is associated with chronic and aggressive periodontitis. *Genes and Immunity* 2010; 11:45-54.
2. Sahingur S, et al. Single nucleotide polymorphisms of pattern recognition receptors and chronic periodontitis. *Journal of Periodontal Research* 2011; 46:184-192.
3. Soga Y, et al. Tumor necrosis factor-alpha gene (TNF-alpha) -1031/-863, -857 single-nucleotide polymorphisms (SNPs) are associated with severe adult periodontitis in Japanese. *Journal of Clinical Periodontology* 2003; 30:524-531.
4. Schroder NJW, et al. Chronic periodontal disease is associated with single-nucleotide polymorphisms of the human TLR4 gene. *Genes and Immunity* 2005; 6: 448-451.
5. Kornman K, et al. The interleukin 1 genotype as a severity factor in adult periodontal disease. *Journal of Clinical Periodontology* 1997; 24:7-77.
6. Wagner J, et al. Prevalence of OPG and IL1 gene polymorphisms in chronic periodontitis. *Journal of Clinical Periodontology* 2007; 34(10):823-827.
7. Taylor J, et al. Cytokine gene polymorphisms and immunoregulation in periodontal disease. *Periodontology* 2000, 2004; 35:158-182.
8. Dias Correa J, et al. Association between polymorphisms in interleukin-17A and 17F genes and chronic periodontal disease. *Mediators of Inflammation* 2012; 2012:1-9
9. Li G, et al. Association of matrix metalloproteinase (MMP)-1, 3, 9, interleukin (IL)-2, 8 and cyclooxygenase (COX)-2 gene polymorphisms with chronic periodontitis in a Chinese population. *Cytokine* 2006; 60:552-560.
10. Letra A. MMP3 and TIMP1 variants contribute to chronic periodontitis and may be implicated in disease progression. *Journal of Clinical Periodontology* 2012; 39:707-716.
11. Internet accessible websites: [www.medterms.com](http://www.medterms.com), <http://medical-dictionary.com>, [www.thefreedictionary.com](http://www.thefreedictionary.com), [www.thefreelibrary.com](http://www.thefreelibrary.com)

**Methodology:** Genomic DNA was subjected to amplification by methods of target enrichment, a version of nested patch PCR, and then sequenced using a MiSeq. The resulting DNA sequences were analyzed using alignment and base call algorithms in the Kailos Blue software. The patient report was created by the review of these analyzed data along with the selection of medical comment and recommendations via TeleGene, a proprietary laboratory information system of Access Genetics, LLC. The analytical and performance characteristics of these laboratory-developed tests (LDT) were determined by Kailos Genetics pursuant to Clinical Laboratory Improvement Amendments (CLIA 88) requirements. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not a requirement prior to use for clinical purposes.

Technical assay performed by Kailos Genetics, Huntsville, AL 855-323-0680

Web enabled system provided by:

