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Review

Regulatory elements and genetic variations in periodontal diseases

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ABSTRACT

Objective: Current evidence suggests that many GWAS and IL1 SNPs are associated with periodontal diseases but their functional role remains ambiguous. Therefore, it is imperative to elucidate the molecular pathways through which these SNPs might act on the development of the disease. The purpose of this review was to highlight the regulatory elements of noncoding regions of the genome and provide insights on the functional role of periodontitis-associated GWAS and IL1 SNPs.
Design: A search was performed using ENCODE data available on different browsers.
Results: GWAS and IL1 SNPs overlap DNase I hypersensitivity sites, histone modifications and transcription binding sites. Some of these noncoding variants influenced the transcription activity of inflammatory genes.
Conclusion: SNPs associated with periodontal diseases may contribute to the development of the disorder through their functional roles. Unraveling the character of genetic components might explain the diversity of clinical phenotypes among population groups as well as disease susceptibility.
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1. Introduction

Periodontal diseases are multifactoriel and complex. Disease susceptibility depends on genetic, environmental and microbiological components (Razzouk & Termechi, 2013). The impact of each component is unknown and most likely depends on every individual. It is estimated that half of the variance in periodontal disease is attributed to genetic factors (Michalowicz et al., 2000). Therefore decoding the genetic material is critical to unravel the molecular pathways underlying the clinical phenotype.

The reference human genome sequence set the stage for studies of genetic variation and its association with human diseases. Genetic and genomic methodologies became essential to discover causative variants relevant to disease pathophysiology. Recently, massively parallel, high-throughput, such as genome-wide association studies (GWAS) and whole genome/exome sequencing, have revolutionized the medical field, identifying the causes of many mendelian and common disorders. GWAS have spat out thousands of spots on the genome in which single nucleotide polymorphisms (SNPs) seem to be associated with complex diseases (NHGRI-EBI/EMBL-EBI GWAS

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Catalog, 2015). However, the causative effect of these genetic markers is not consistent across multiple ethnicities, therefore most of them may not be informative in different population groups. One plausible hypothesis of this divergence is related to the SNPs' location in the genome and its potential function that generate an effect in one individual and not in the other. Genetic mapping showed that the vast majority of GWAS-identified disease- and trait-associated SNPs fall within noncoding regions of the genome (Maurano et al., 2012). In fact, 88% of associated SNPs are either intronic or intergenic, while only 5–10% of them occur within the exonic region (Hindorff et al., 2009; Maurano et al., 2012). Thus, it is highly probable that the underlying mechanism linking these SNPs to the corresponding phenotype is regulatory.

The noncoding DNA represents 98% of the human genome. Much of this DNA has a functional implication and is involved in the regulation of coding genes (ENCODE Project Consortium, 2011, 2012). Recent evidences showed that individuals' medical histories could be predicted by their noncoding genomes (Guturu, Chinchali, Clarke, & Bejerano, 2016). The importance of these areas has been highlighted by the Encyclopedia of DNA Elements (ENCODE) project and NIH Roadmap Epigenomics Program (ENCODE project, 2015; NIH Roadmap Epigenomics Program, 2015). The ENCODE project is an international consortium with the main goal of annotating regions of the genome. In particular, its purpose is to identify and catalogue the *cis*-regulatory regions that are bound by DNA- and RNA-binding proteins, the chromatin structure and histone modifications, map DNase I hypersensitive sites, measure transcriptional activity and quantify the extend of DNA methylation. *cis*-regulatory regions include diverse functional elements (e.g. promoters, enhancers, silencers, and insulators) that collectively modulate the magnitude, timing, and cell-specificity of gene expression. Many different approaches are being used to reveal these functional sequences such as RNA-seq (for RNA transcribed regions), ChIP-seq and DNase-seq (for transcription factors-binding sites) and DNase-seq and FAIRE-seq (for chromatin structure). And most of these experiments were performed using different cell lines (e.g. GM12878, H1-hESC, K562, HUVEC, HSMM, NHLF, NHEK cell lines). The outcome data revealed that 80.4% of the human genome displays some functionality in at least one cell type (ENCODE Project Consortium, 2012). To date, ENCODE project has generated over 4000 experiments across more than 350 cell lines and tissues.

Since GWAS analyses typically associate diseases to SNPs in large regions, comparison to ENCODE noncoding regulatory elements can help pinpoint putative causal variants with a functional role. Thus, the involvement of these variants in the pathogenesis of diseases may depend on the nature of their occupation in the genome. Few publicly databases are available for researchers and clinicians such as the UCSC genome browser, where the genetic data is integrated with ENCODE data of gene regulation to try to identify candidate functional variants among the disease-associated SNPs (UCSC Genome Browser, 2015). It is noteworthy to point out that most GWAS SNPs are "tagged" SNPs, thus recognizing all other linked variants on the same haplotype; in nearly all cases, they are not considered directly causative for the disease. The SNP most likely to play a functional role according to ENCODE evidence is not the reported association, but a different SNP in strong linkage disequilibrium (LD) with the reported association Schaub, Boyle, Kundaje, Batzoglou, and Snyder (2012).

Disease association studies have estimated that there are hundreds of human periodontitis-associated GWAS SNPs (Table 1). However, very few have identified SNPs with significance of association. Recent publication has shown enhanced GWAS results after creating distinct periodontal complex traits combining clinical data with subgingival microbial composition data and biomarkers of the tissue inflammatory response (Offenbacher et al., 2016). Also, candidate-gene experiments have established that IL-1 gene cluster polymorphisms are associated with increased susceptibility to a number of inflammatory diseases including periodontitis. Here, we briefly highlight the main regulatory elements of the genome and illustrate the possible genomic function of GWAS- and most common IL-1 SNPs associated with periodontal diseases, using ENCODE data.

2. Epigenetic landmarks

2.1. Histone modifications

Biochemical modifications (e.g. methylation or acetylation) of the histone proteins present in chromatin influence gene expression by changing how accessible the chromatin is to transcription factors (Heintzman et al., 2009). There are some specific histone modifications or combination of modifications that confer unique biological functions to the region of the genome. For example, H3K4m3 and H3K9ac are considered to be marks of active or potentially active promoter regions, H3K4m1 and H3K27ac marks of active or potentially active enhancer regions, H3K36m3 and H3K79m2 marks of transcriptional elongation, and H3K27m3 and H3K9m3 marks of inactive regions (Bernstein et al., 2005; Heintzman et al., 2007; Siggens & Ekwall, 2014). To date, ENCODE has sampled 13 of more than 60 currently known histone or DNA modifications across 147 cell types. Previous studies showed that

Table 1
GWAS for periodontal diseases.

References	Total SNPs reported	Intronic	Intergenic	Exonic/5′UTR/3′UTR	SNPs with p value $<10-7$
Shimizu et al. (2015)	2	2			
Freitag-Wolf et al. (2014)	1		1		
Feng et al. (2014)	2	1	1		
Shaffer et al. (2014)	10	4	6		
Divaris et al. (2013)	3	1	2		rs2521634 rs7762544 rs3826782
Teumer et al. (2013)					
DPAL	15	8	6	1	
CDC/AAP	26	15	8	3	rs13237474 rs6802315 rs13145041
PAL4Q3	16	8	8		rs7567687 rs1370967
Mean PAL	36	17	18	1	rs9979250 rs77490164
Divaris et al. (2012)	15	5	9	1	rs11800854 rs11621969 rs10760187
Schaefer et al. (2010)	1	1			**rs1537415**

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