

before the age of puberty and in other individuals between puberty and age 18. The genetic factors that were identified in those cases involved very overt biologic mechanisms that most likely would predispose the individual to multiple health problems. To date, efforts to find the same types of genetic factors in adult forms of periodontitis have not been successful.

Genetic testing for disease prediction has been made possible (see U.S. Pat. Nos. 4,582,788 and 5,110,920) for diseases associated with or caused by one to two genes, once the genes are identified, to determine the risk of a person carrying a given gene for the disease (see for example U.S. Pat. Nos. 4,801,531, 4,666,828 and 5,268,267).

A genetic testing kit was developed to predicts risk for periodontal diseases using two variations in the human genome, one located in IL1A gene (IL1A +4845) and the other in IL1B gene (IL1B +3954). Carriers of at least one copy of the minor allele in each of these gene variations have increased susceptibility to periodontal disease. See U.S. Patent No. 5,686,246. However, such a test has a limited utility in some ethnic populations and the test identifies only a small portion of people who are at risk for periodontal diseases in those populations. There is the need to find more sensitive method of determining risks of periodontal disease in all ethnic populations.

BRIEF SUMMARY OF THE INVENTION

In one aspect, there is provided a method of determining whether a patient is predisposed to having severe periodontal disease and/or having high risk of progression of periodontal disease, comprising the steps of:

- (i) genotyping a biological sample obtained from the patient for genetic polymorphism pattern comprising IL 1B (rs16944), IL 1B (rs1143623) IL 1B (rs4848306), and IL 1B (rs1143633);
- (ii) comparing said genetic polymorphism pattern to a reference composite genotype pattern, wherein the similarity of said genetic polymorphism pattern to said reference pattern indicate said patient's predisposition to having severe periodontal disease and/or having high risk of progression of periodontal disease,

wherein said reference composite genotype pattern is selected from the group consisting of

- a. one copy of IL1B (rs16944; C/T) allele 1 (C), one copy of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);

- b. two copies of IL1B (rs16944; C/T) allele 2 (T), one copy of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
- c. two copies of IL1B (rs16944; C/T) allele 2 (T), one copy of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and one or two copies of IL1B (rs1143633; G/A) allele 2 (A);
- d. two copies of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
- e. two copies of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and one or two copies of IL1B (rs1143633; G/A) allele 2 (A);
- f. one copy of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
- g. one copy of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and one or two copies of IL1B (rs1143633; G/A) allele 2 (A);
- h. two copies of IL1B (rs16944; C/T) allele 2 (T), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
- i. two copies of IL1B (rs16944; C/T) allele 2 (T), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and one or two copies of IL1B (rs1143633; G/A) allele 2 (A);
- j. two copies of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 2 (T), and two copies of IL1B (rs1143633; G/A) allele 1 (G); and
- k. one copy of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), one copy of IL1B (rs4848306; C/T) allele 2 (T), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
- l. two copies of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), one copy of IL1B (rs4848306; C/T) allele 2 (T) and one copy of allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G); and

m. two copies of IL1B (rs16944; C/T) allele 2 (T), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G).

In another aspect, there is provided a method of determining whether a patient has a high risk of progression of periodontal disease, comprising the steps of:

- (i) selecting a patient presenting a sign of a periodontal disorder;
- (ii) isolating a nucleic acid sample from a biological sample obtained from said patient;
- (iii) contacting the nucleic acid sample with one or more primers that specifically hybridise 5' and 3' of at least one allele of an ILB locus haplotype comprising single nucleotide polymorphism (SNP) IL IB (rs16944; C/T), IL IB (rs 1143623; G/C), IL IB (rs4848306; C/T), and IL IB (rs1143633);
- (iv) detecting the number of copies of allele 1 and allele 2 of each of said SNPs IL IB (rs16944; C/T), IL IB (rs 1143623; G/C), IL IB (rs4848306; C/T), and IL IB (rs1143633);
- (v) assigning a composite genotype to the patient based upon the alleles detected in step (iv); and
- (vi) classifying said patient into a periodontal disease risk progression group based on analysis of said alleles of said SNPs detected in step (iv), wherein a patient with a composite genotype selected from the group consisting of:
 - a. one copy of IL1B (rs16944; C/T) allele 1 (C), one copy of IL1B (rs1143623; G/C) allele 1 (G); two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
 - b. two copies of IL1B (rs16944; C/T) allele 2 (T), one copy of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C)), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
 - c. two copies of IL1B (rs16944; C/T) allele 2 (T), one copy of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and one or two copies of IL1B (rs1143633; G/A) allele 2 (A);
 - d. two copies of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (g) two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
 - e. two copies of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and one or two copies of IL1B (rs1143633; G/A) allele 2 (A);

- f. one copy of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
- g. one copy of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and one or two copies of IL1B (rs1143633; G/A) allele 2 (A);
- h. two copies of IL1B (rs16944; C/T) allele 2 (T), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
- i. two copies of IL1B (rs16944; C/T) allele 2 (T), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and one or two copies of IL1B (rs1143633; G/A) allele 2 (A);
- j. two copies of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 2 (T), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
- k. one copy of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), one copy of IL1B (rs4848306; C/T) allele 2 (T), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
- l. two copies of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), one copy of IL1B (rs4848306; C/T) allele 2 (T) and one copy of allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G); and
- m. two copies of IL1B (rs16944; C/T) allele 2 (T), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);

is classified at being at a high risk of progression of periodontal disease.

The present ~~invention~~disclosure is directed to a method of determining whether a patient is predisposed to having severe periodontal disease and/or having high risk of progression of periodontal disease, comprising the steps of (i) taking a biological sample from said patient; (ii) genotyping said biological sample for genetic polymorphism pattern comprising IL 1B (rs16944), IL 1B (rs1143623) and IL 1B (rs4848306); and (iii) comparing said genetic polymorphism patterns to a reference composite genotype pattern; wherein the similarity of said genetic polymorphism patterns to said reference pattern indicate said patient's

predisposition to having severe periodontal disease and/or having high risk of progression of periodontal disease.

In yet another aspect, there is provided a testing kit for determining whether a patient is predisposed to having severe periodontal disease and/or having high risk of progression of periodontal disease, comprising:

(i) one or more primers for determining the number of copies of allele 1 and allele 2 of each of the IL 1B single-nucleotide polymorphisms (SNPs) comprising IL1B (rs16944; C/T), IL1B (rs1143623; G/C), IL1B (rs4848306; C/T) , and IL1B (rs1143633);

(ii) a control sample as a reference, and

(iii) an instruction, wherein said instruction classifies said patient as having high risk of progression of periodontal disease when said patient has a composite genotype selected from the group consisting of

a. one copy of IL1B (rs16944; C/T) allele 1 (C), one copy of IL1B (rs1143623; G/C) allele 1 (G); two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);

b. two copies of IL1B (rs16944; C/T) allele 2 (T), one copy of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);

c. two copies of IL1B (rs16944; C/T) allele 2 (T), one copy of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and one or two copies of IL1B (rs1143633; G/A) allele 2 (A);

d. two copies of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G) two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);

e. two copies of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and one or two copies of IL1B (rs1143633; G/A) allele 2 (A);

f. one copy of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G) two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);

- g. one copy of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and one or two copies of IL1B (rs1143633; G/A) allele 2 (A);
- h. two copies of IL1B (rs16944; C/T) allele 2 (T), two copies of IL1B (rs1143623; G/C) allele 1 (G) two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
- i. two copies of IL1B (rs16944; C/T) allele 2 (T), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and one or two copies of IL1B (rs1143633; G/A) allele 2 (A);
- j. two copies of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 2 (T), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
- k. one copy of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), one copy of IL1B (rs4848306; C/T) allele 2 (T), and two copies of IL1B (rs1143633; G/A) allele 1 (G);
- l. two copies of IL1B (rs16944; C/T) allele 1 (C), two copies of IL1B (rs1143623; G/C) allele 1 (G), one copy of IL1B (rs4848306; C/T) allele 2 (T) and one copy of allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G); and
- m. two copies of IL1B (rs16944; C/T) allele 2 (T), two copies of IL1B (rs1143623; G/C) allele 1 (G), two copies of IL1B (rs4848306; C/T) allele 1 (C), and two copies of IL1B (rs1143633; G/A) allele 1 (G).

In yet another aspect, there is provided a testing kit for determining whether a patient has high risk of progression of periodontal disease, comprising:

- (i) one or more primers for determining the number of copies of allele 1 and allele 2 of each of the IL1B single nucleotide polymorphisms (SNPs) comprising IL 1B (rs16944; C/T), IL 1B (rs1143623; G/C) IL 1B (rs4848306; C/T), and IL 1B (rs1143633);
- (ii) a control sample as a reference; and
- (iii) instructions for carrying out the method as described herein.

The present ~~invention~~disclosure is also directed to a testing kit for determining whether a patient is predisposed to having severe periodontal disease and/or having high risk of progression of periodontal disease, comprising (i) biological sample collection means; (ii) a means for