Genetic Susceptibility to Dental Implant Failure: A Critical Review

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The observation that clinical factors alone do not explain why some patients develop implant loss; the understanding of the osseointegrated implant failure as a complex, multifactorial process; and the observed aggregation of repetitive failure in certain individuals raise interesting questions related to host susceptibility to dental implant failure. Genetic analysis applied to dental implants began in the late 1990s, and since then, increased interest in genetic susceptibility to the phenotype has been demonstrated by several studies. These studies, however, have been based on and limited to candidate gene association analysis and were intended to find associations between specific alleles and/or genotypes of genetic markers and susceptibility to implant failure. The aim of this review is to provide a brief description of the current methodology for genetic analysis of complex traits, followed by a comprehensive review of the literature related to genetic susceptibility to dental implant failure and a discussion of different aspects of the applied methodology. Moreover, a novel approach of genome wide, case-control analysis is discussed as an alternative method to access genetic influence to dental implant failure mechanisms. Advances toward the elucidation of the genetic basis of dental implant loss may contribute to the understanding of why some patients do not respond to currently available treatments while others do and provide potential targets for effective screening, prevention, and treatment. For example, clinicians might be able to estimate, before the elective surgical procedure, the risk of a given patient to develop a negative individual host response. Int J Oral Maxillofac Implants 2008;23:409–416

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Osseointegrated dental implants are fixtures, commonly of titanium, which are surgically screwed into the jaw bone. After the surgery, a traditional, 2-step technique requires a healing phase of 90 to 180 days without submitting the implant to mechanical masticatory forces. Only after the healing phase, the prosthesis (crown) is attached to the implant and submitted to occlusal load. In an alternative, 1-step, immediate-load technique, the healing processes occur in the presence of masticatory forces. In both cases, the implant is expected to functionally and structurally connect to the bone in a process known as osseointegration.[1] The mechanism of osseointegration of dental implants is very similar to primary bone healing. First, the inflammatory process promoted by surgical trauma causes circulatory alterations and hematoma. Then regeneration takes place, with the wound being substituted by bone tissue in a remodeling process that leads to wound maturation.[2] Therefore, successful implant osseointegration is likely to depend on factors such as an appropriate tissue repair mechanism[3] and adequate immunologic response.[4]

Dental implantation is a very predictable procedure that often provides the best result for dental replacement of patients who present with missing teeth.[5,6] In spite of a success rate of more than 90%,

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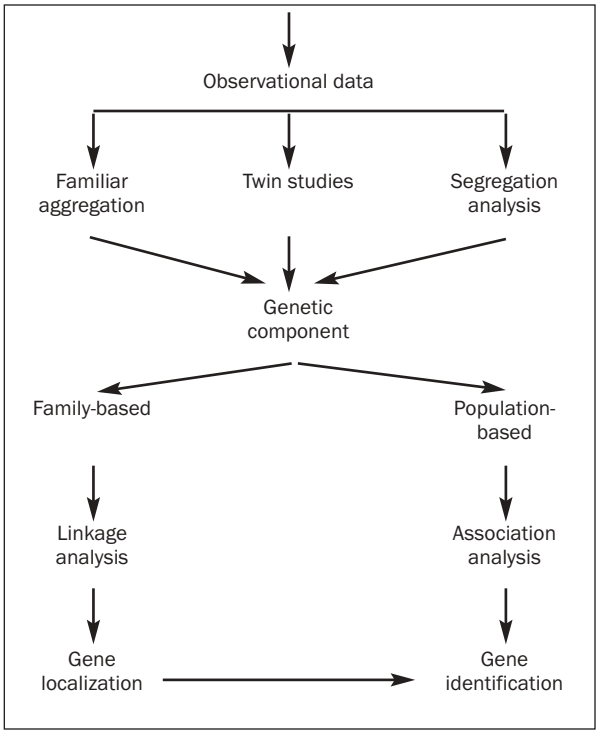

Fig 1 Suggested flow chart combining different strategies for genetic analysis of complex traits, from the detection of a genetic component to the identification of the functional gene variants.

the absolute number of dental implant failures is significant given that approximately 1 million procedures are conducted annually worldwide.[7] Dental implant osseointegration failure is a complex, multifactorial trait that has been investigated by several clinical follow-up and retrospective studies.[6,8,9] The process is divided into early and late events: early failure occurs before implant load, and late failure takes place after the implant has received occlusal loading.[10] Early failures have been related to smoking,[11] aging,[12] systemic diseases,[13,14] bone quantity and quality,[15–17] surgical trauma,[18] and contamination during the surgical procedure.[19,20] Late failures have been related to peri-implantitis[17] and occlusal overload.[21]

Although these previous studies have provided an important contribution to the understanding of the implant failure process, in some situations, clinical factors alone do not explain why some patients develop implant loss.[22] Moreover, the occurrence of implant failures is not randomly distributed in treated populations; multiple implant losses are likely to occur in specific high-risk individuals, a phenomenon termed *clusterization,*[23] and reoccurrence of implant failure is frequently observed.[14,24] Taken together, these observations strongly suggest the existence of genetic risk factors for dental implant loss.[25]

GENETIC ANALYSIS OF COMPLEX TRAITS

Complex traits result from an interaction between 1 or more genetic variants and environmental or nongenetic risk factors.[26] When studying complex traits, the existence of multiple loci affecting the disorder is generally expected.[27] Classically, the first goal of a genetic study involving a complex trait is to detect a genetic component from observational data. This can be achieved by applying several different strategies, such as the observation of familiar aggregation of cases or the clusterization phenomenon, in cases where access to pedigrees is limited. Another powerful tool is twin studies, in which the concordance rate of a trait is estimated and compared among monozygotic and dizygotic twins. Finally, complex segregation analysis can be used to describe the mode of inheritance that provides the best fit, given the observed pedigree data. Unfortunately, none of these approaches provide information about the exact nature of the genetic component, such as number, location, and identity of the genes involved; therefore, further studies are necessary, typically involving 2 main strategies: linkage analysis and association analysis. Fig 1 shows the usual pathway one might follow from detecting a genetic component to the identification of the gene variants responsible for the studied complex phenotype.

Linkage analysis is a genomic region hunting technique that traces patterns of cosegregation of the trait and specific genomic segments in high-risk, multiple affected pedigrees.[28] The goal is to physically locate a disease-causing gene within the narrowest possible genomic interval. Genes are located based solely on their position in the genome. Modern linkage analysis is a powerful approach for studying both mendelian and complex genetic disorders.[29] It is suitable for large candidate region analysis or even genome-wide searches.[30,31] Results are usually expressed as a logarithm of odds (LOD scores); it is generally accepted that statistical significance is reached when the LOD score is higher than 3.0 for candidate region analysis and 3.3 for genome-wide studies.[32,33] The most important limitations of linkage analysis are *(1)* the need to enroll multiple affected pedigrees, which may be difficult to obtain in cases of rare or late-onset diseases; *(2)* low power to detect genes exerting moderate to low effect over the phenotype[34]; *(3)* the difficulty of replication of positive linkage; and *(4)* low power to pinpoint the exact gene/variation causing the linkage effect.[35] In fact, linkage analysis of complex traits often results in the identification of a genomic region several megabases long and containing a large number of genes. In these cases, narrowing down the candidate

genomic region is usually attempted through association analysis.

Association analysis is based on the comparison of the allele frequencies of a genetic marker across affected and unaffected individuals. This can be done in a family-based or population-based (case-control) sample. A given allele is considered to be associated with the disease if that allele occurs at a significantly higher frequency among affected as compared to unaffected individuals.[36] The strategy is commonly used for candidate gene analysis, with the candidate genes usually defined based on their possible role on disease physiopathology (functional candidates), by previous linkage analysis (positional candidates), or both. Association analysis is more powerful than linkage analysis for the detection of genetic effects with low to moderate genotypic relative risk.[31] However, since the association effect extends over very short genomic segments, the strategy is not as suitable as linkage analysis for large genomic region or genome-wide screening; several hundreds of thousands of markers would be required for a reliable genome-wide coverage. In addition, the need of large sample sizes, small *P* values, and replication in independent samples have been advocated as reliability parameters for true association.[37] Moreover, in population-based, case-control studies, patients may differ from the control group in their genetic background, introducing variables unrelated to the disease and causing a type of spurious association or confounding named *population stratification*.[38,39]

Encouraged by the early success in the identification of genes responsible for monogenic diseases, many investigators have embraced different strategies for the dissection of the genetic component controlling complex diseases.[40] For example, a 2-step study using hypothesis-generating, genome-wide linkage analysis followed by association-based, fine mapping of the candidate regions identified has resulted in the first positional cloning of genetic variants associated with an infectious disease.[41] However, the knowledge about the genetic mechanisms controlling complex traits is still fragmented and incomplete, and little is known about genetic susceptibility to most physiopathologic processes.[4]

Genetic Analysis of Dental Implant Failures

Interindividual variability to different phenotypes is partially determined by the human genetic code. Specifically, variability is due to the existence of a large number of polymorphisms, gene sequence variations with minimum allele frequency higher than 1% in the population distributed evenly throughout the entire genome.[42] Polymorphisms have been shown to modulate host response and susceptibility to numerous diseases.[43–46] A polymorphism is said to be "functional" if it modulates gene expression or results in an amino acid change in the polypeptide chain.[45] Alternatively, a polymorphism is defined as "silent" if no obvious, predictable biologic impact can be inferred.[47] Independent of their functional impact, polymorphisms can be used as gene markers for genetic analysis, and several cases of association between functional and silent polymorphisms have been observed.

The focus of studies investigating genetic susceptibility to dental implant failure has been limited to candidate gene association analysis.[18,48–51] In this approach, selected genes are defined as candidates based on available information about the osseointegration process. Incomplete biologic knowledge of the involved metabolic pathways, however, limits the search to a fraction of all the correlated genes. In these studies, functional polymorphisms, especially those that modulate the correspondent protein expression rate, are frequently chosen.

The most commonly studied functional polymorphisms for dental implant failure are variations of the interleukin-1 (IL-1) gene cluster, in particular in the IL-α *(IL1A)* and IL-1β *(IL1B)* genes. Because of IL-1 proinflammatory and bone resorbing properties,[52,53] a role has been suggested for this cytokine in controlling the risk of severe chronic periodontitis development.[54] Also, a role for IL-1 in dental implant success was proposed.[55] However, evidence for association has been found between *IL1A* and *IL1B* gene polymorphisms (allele T for both *IL1A*-889 and *IL1B*+3953 polymorphisms, called "positive genotype") and periodontal disease[54] but not implant failure.[56] A statistically insignificant evidence of an increased risk to implant failure in patients with specific *IL1A* and *IL1B* genotypes has been reported for different populations.[57,58] Otherwise, in a partially edentulous group treated for periodontal disease prior to implant treatment, a synergistic effect between the *IL1* positive genotype and smoking was detected,[59] and individuals with these 2 conditions together were characterized as a high-risk population for implant failure. Moreover, studies comparing smoking and nonsmoking groups detected an increased risk for peri-implant bone loss in a heavy smoking population with *IL1A* and *IL1B* polymorphisms during the after-loading phase.[18,49,60]

Interleukin-2 (IL-2) is a cytokine involved in the B-cell activation. It stimulates macrophages, natural killer cells, and T-cell proliferation, which mediate the cellular immune response; thus, it is regarded as a proinflammatory cytokine.[61–63] Interleukin-2 has been also implicated in the stimulation of osteoclast activity in bone resorption.[64] Interleukin-6 (IL-6) plays a role in B-cell differentiation and T-cell prolifer-

Table 1 A Summary of Association Studies Between Genetic Polymorphisms and Osseointegrated Dental Implant Failures in Different Populations

Authors	Year	Polymorphisms	Case (n)/ Control (n)	Mean age (y)	Smoking Yes/No	Population	Results
Rogers et al[56]	2002	*IL1A* (-889) and *IL1B* (+3953)	19/31	66	?	Australian Caucasian	Not associated with implant failure
Wilson and Nunn[58]	1999	*IL1A* (-889) and *IL1B* (+3953)	27/38	57	27/35	?	Not associated with implant failure
Campos et al[57]	2005b	*IL1A* (-889), *IL1B* (-511, +3953), and IL1RN (intron 2 - 86 bp repeats)	28/34	47.5	0/62	Brazilian	Not associated with early implant failure
Feloutzis et al[60]	2003	*IL1A* (+4845) and *IL1B* (+3954)	?	59.5	41/39	European Caucasian	Smoking + IL1 positive genotype associated with marginal bone loss
Gruica et al[18]	2004	*IL1A* (+4845) and *IL1B* (+3954)	34/146	*	53/127	European Caucasian	Smoking + IL1 positive genotype associated with late infection
Jansson et al[59]	2005	*IL1A* (-889) *IL1B* (+3954)	6/16	54	10/12	European Caucasian	Smoking + IL1 positive genotype associated with implant loss
Shimpuku et al[49]	2003b	*IL1A* (-889) and *IL1B* (-511, +3954)	17/22	55.1	14/25	Japanese	Associated with marginal bone loss
Campos et al[65]	2005a	*IL2* (-330) and *IL6* (-174)	34/40	46.3	0/74	Brazilian	Not associated with early implant failure
Campos et al[48]	2004	*TNFA* (-308)	28/38	47.2	0/66	Brazilian	Not associated with early implant failure
Santos et al[51]	2004a	*TGFB1* (-509, -800)	28/40	46	0/68	Brazilian	Not associated with early implant failure
Santos et al[50]	2004b	*MMP1* (-1607) and *MMP9* (-1562)	20/26	45.9	0/46	Brazilian	MMP1 - associated, and MMP9 - not associated with implant failure
Shimpuku et al[66]	2003a	*BMP4* (+538)	21/36	52.6	24/38	Japanese	Associated with marginal bone loss
Nosaka et al[67]	2002	*CTR* (+1377)	15/20	54.8	15/20	Japanese	Associated with marginal bone loss in mandible, but not in maxilla

*Age range, 25 to 90 years; ? means data unknown.

ation.[68] It also stimulates hematopoiesis[69] and accelerates bone resorption.[70] In spite of the association between IL2 and IL6 promoter polymorphisms and periodontal disease,[71,72] no significant differences in the distribution of those polymorphisms were found between implant failure and control groups in a Brazilian population.[65]

Tumor necrosis factor-α (TNF-α) is a potent mediator of immune-inflammatory response[73,74] and also has been reported to induce bone resorption in vitro and in vivo.[75,76] The *TNFA* (G-308A) gene polymorphism was investigated and showed no association with early implant failure.[48]

No association was also found between early osseointegrated implant failure and polymorphisms in the transforming growth factor beta-1 (TGF-β1) gene.[51] This last cytokine is a multifunctional protein known to induce the expression of collagen genes, to provoke extracellular matrix fibrosis, and to regulate cell growth, differentiation, and function.[77]

Matrix metalloproteinases (MMPs) are a family of metal-dependent proteolytic enzymes which mediate the degradation of extracellular matrix and basement membranes in several tissues.[78] MMPs are likely to be involved in the dental implant osseointegration process.[79,80] Polymorphisms that increase transcriptional activity of MMP-1 and MMP-9 were analyzed, and allele and genotype frequencies were compared between the failure and control groups. Results showed that *MMP1* polymorphisms were associated with implant failure, while no association with implant loss was found for the *MMP9* promoter region polymorphism.[50]

Polymorphisms in genes involved in bone metabolism have also been investigated. A polymorphism in the bone morphogenetic protein-4 (BMP-4) gene was associated with marginal bone loss before second-stage surgery (implant loading).[66] A positive correlation was also observed between a calcitonin receptor (CTR) gene polymorphism and marginal

Table 2 Functional Impact of the Polymorphisms Investigated for Susceptibility to Implant Failure

Authors	Year	Polymorphisms	Functional	Type of Functionality
Dominici et al[81]	2002	IL1A (C-889T)	Yes	Regulation of gene expression
Cox et al[82]	1998	IL1A (G+4845T)	-	99% linkage disequilibrium with IL1A (-889)
Pociot et al[83]	1992	IL1B (C+3953/4T)	Yes	Regulation of gene expression
Hu et al[84]	2005	IL1RN (inton 2 to 86 bp repeats)	Yes	Regulation of gene expression
Hoffmann et al[85]	2001	IL2 (T-330G)	Yes	Regulation of gene expression
Fishman et al[86]	1998	IL6 (G-174C)	Yes	Regulation of gene expression
Hajeer and Hutchinson[87]	2001	TNFA (G-308A)	Yes	Regulation of gene expression
Kim et al[77]	1989	TGFB1 (C-509T)	Yes	Regulation of gene expression
Kim et al[77]	1989	TGFB1 (G-800A)	Yes	Regulation of gene expression
Rutter et al[88]	1998	MMP1 (G-1607GG)	Yes	Regulation of gene expression
Zhang et al[89]	1999	MMP9 (C-1562T)	Yes	Regulation of gene expression
Mangino et al[90]	1999	BMP4 (T+538C)	Yes	Amino acid change Val147Ala
Nakamura et al[91]	1997	CTR (C+1377T)	Yes	Amino acid change Pro463Leu

bone loss at second-stage surgery.[67] A summary of studies investigating the association between genetic polymorphisms and osseointegrated dental implant failure in different populations is shown in Table 1. The functional impact of the polymorphisms investigated for susceptibility to implant failure is shown in Table 2.

Despite these promising advances, the exact number, identity, and role of regulatory factors that lead to a successful implant osseointegration and its maintenance are still largely unknown, which limits genetic analysis approaches based on functional candidate genes. The challenge then is to map all the involved genes,[40] a considerably difficult task given that the human genome is composed of 22 pairs of autosomal chromosomes and 1 pair of sexual chromosomes carrying at least 30,000 genes.[92]

FUTURE PERSPECTIVES

Although candidate gene association analysis has proved to be a promising tool for the dissection of the exact nature of the genetic component controlling dental implant failure, the design is limited by the fact that just a small segment of the genome is analyzed. Candidate gene approach is limited in providing a genome-wide perspective on interesting gene regions and gene-to-gene interactions. In addition, the sample sizes are often small; therefore, findings must be replicated in larger populations. Finally, larger-scale studies, such as genome-wide linkage analysis, are made difficult by the need of large samples of multiple affected pedigrees. As a consequence, genetic susceptibility to osseointegrated implant failure remains widely unknown.

All the studies mentioned thus far employed single-nucleotide polymorphisms (SNPs) as gene markers. SNPs are the most frequently observed type of genetic polymorphisms. Catalogued SNPs in public databases have grown from 1.4 million in 1999[93] to 2.1 million in 2001[94] and up to approximately 4.1 million markers available in SNP public databases today.[95] Though somewhat less informative than other types of DNA markers, SNPs are technically easier and less expensive to genotype. As a recent development, DNA microarrays are a new, fully automated technology that allows genotyping hundreds of thousands of SNPs in a single experiment.[96] This new, extremely high throughput SNP genotyping technology is making possible, for the first time, the development of association-based genome-wide scans using case-control samples to investigate genes related to complex traits such as Parkinson disease.[97] These whole-genome association studies, using hundreds of thousands of SNPs covering the entire genome, combine the best features of linkage analysis with the strength of association analysis.[98] In this new approach, classic, family-based linkage analysis would not be necessary, making it possible to study population samples of unrelated subjects. This feature is particularly interesting in the context of dental implant failure, where the difficulty of enrolling multiple-case families poses a major obstacle for the application of family-based linkage tools.

However, some limitations exist. Association-based genome-wide studies are still very expensive and are limited to laboratories equipped with cutting-edge genotyping technology.[99] Also, as mentioned already, population-based association analyses always involve the risk of cryptic, undetected population stratification leading to spurious results. Finally, the generation of such a tremendous amount of raw data demands the development of adequate

methods of statistical analysis.[38] Furthermore, due to the large number of tests performed, false-positive results are likely to increase.[89] In this context, replication of the original findings in independent populations becomes mandatory.[90]

Despite the difficulties, the motivation to continue to apply traditional and new approaches of genetic analysis to the effort toward a better understanding of dental implant failure mechanisms is clear. Genetic studies may shed new light not only upon the physiopathology of dental implant failure but also upon broader, related processes, such as bone healing. In addition, a direct result of such studies may be the definition of potential targets for effective screening, prevention, and maintenance of dental implants.

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