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Aggressive periodontitis is likely influenced by a few small effect genes

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Abstract

Aim: To evaluate the inheritance mode of aggressive periodontitis in a collection of families with a similar geographic origin.

Materials and Methods: Segregation analysis was performed in pedigree data from 74 families by the use of the SEGREG program of SAGE v.5.4.2. Homogeneous no transmission, homogeneous Mendelian transmission, homogeneous general transmission, semi-general transmission and heterogeneous general transmission models were tested assuming the prevalence of aggressive periodontitis as 1% and no deviations from Hardy–Weinberg equilibrium. The parameters of the model were estimated by the method of maximum likelihood, which provides the overall ln (likelihood), -2ln and the AIC (Akaike's score) for each model. The likelihood ratio test (LRT) was used to compare each model against a fully general model ($p > 0.05$).

Results: The most parsimonious mode of inheritance was the semi-general transmission model that allows the heterozygote transmission probability to vary.

Conclusion: This result provides strong support for the hypothesis that genetic factors play a role in aggressive periodontitis and that a few loci, each with relatively small effects, contribute to aggressive periodontitis, with or without interaction with environmental factors.

Key words: familial aggregation; genetics; inheritance; periodontitis; segregation analysis

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Patients with aggressive periodontitis are characterized by a rapid and severe periodontal destruction around molars and/or incisors, which can become generalized and affect adjacent teeth when not treated. Clinical signs and the onset of the disease can be seen around puberty, but the infection around first molars is thought to happen at an earlier age. Epidemiological surveys have shown that the prevalence of aggressive periodontitis varies among ethnic groups, regions and countries and may range from 0.1% to 15% (Albandar et al. 1997). A greater prevalence is reported in Africans and African-descendent groups than it is in Caucasians and Hispanics (Loe & Brown 1991). Aggressive periodontitis shows remarkable familial aggregation (Novak & Novak 1996). It seems to be inherited in a Mendelian manner, and both autosomal modes (Long et al. 1987, Marazita et al. 1994) and X-linked transmission (Hart et al. 1992) have been proposed. Although the genetic models may differ, there is a consensus that genetics play an important role in aggressive periodontitis.

To investigate the role of genetic and environmental influences on aggressive periodontitis, we tested a series of Mendelian segregation models, which were fitted in the presence of residual familial correlation using the SEGREG program, as implemented in SAGE v.5.4.2 (S. A. G. E. 2008). These models assume that a variation in the phenotype among individuals is the result of a major gene effect, and of polygenic and residual variations, which could create familial correlations and random individual variation. Family-based designs provide the opportunity to study variation in the phenotype and provide evidence that justifies future family-based genetic analysis. From these approaches comes the possibility to localize the disease loci through linkage analysis of observed polymorphisms (Elston 1992).

Conflict of interest and source of funding statement

The authors declare that there are no conflicts in this study.
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Materials and Methods

Seventy-four probands with aggressive periodontitis were identified and recruited at the Periodontology Department at the Rio de Janeiro State University, in the city of Rio de Janeiro, and UNIGRANRID in the city of Duque de Caxias, both in the state of Rio de Janeiro, Brazil. Diagnosis of aggressive periodontitis was based on the 1999 Consensus Classification of Periodontal Diseases (Armitage 1999). In brief, individuals with 10 or more teeth with interproximal sites with at least 4 mm of clinical attachment loss and at least 4 mm pocket depth (two of these teeth must be first molars showing at least 5 mm of clinical attachment loss and at least 4 mm of probing pocket depth) and radiographic evidence of advanced alveolar bone loss were defined as generalized aggressive periodontitis. Localized aggressive periodontitis was the clinical diagnosis if the individuals had fewer than 10 teeth with inter-proximal sites with the same criteria presented above. Incipient aggressive periodontitis was the definition for individuals that had two or more first molars showing at least 4 mm of clinical attachment loss and at least 3 mm of probing pocket depth and radiographic evidence of alveolar bone loss. All individuals diagnosed with any of the three types of aggressive periodontitis described above were considered as affected in this study. If individuals were edentulous and reported having lost all their teeth at young age (before 35 years), for no obvious reasons such as trauma or extensive cavities, this was recognized as a potential indicator that they started as an aggressive periodontitis case and we also designated them as affected. In addition, the following information was collected by the same examiner from all probands and family members: affection status, gender, age, family relationship and ethnicity, cigarette smoking habits, current medications taken and general health status. In addition, clinical data (pocket probing depth and clinical attachment level) and radiological examinations were collected from all participants. Individuals with co-existing morbidities (e.g. diabetes) or smokers were not defined as affected to minimize the risk of inadvertently including chronic periodontitis in the analysis.

The study sample of 74 families, comprised of 475 individuals (average 6.4 individuals per family), is summarized in Tables 1 and 2. The male:female ratio was 0.8, with 217 males and 258 females. Fifty-four of these families have obvious African ascendency. The study protocol was approved by both the Ethical Committee of the Rio de Janeiro State University and University of Pittsburgh, and informed consent was obtained from all individuals prior any research activity.

Table 1. Numbers of Individuals by phenotype and gender in 74 families with at least a proband affected with aggressive periodontitis

Phenotype and gender	Number of individuals
Affected	
Male	55
Female	97
Unaffected	
Male	162
Female	161
Total	475

Table 2. Distribution of aggressive periodontitis individuals across pedigrees and pedigrees size range

Number of affected/pedigree	Number of pedigrees	Pedigree size (range)
1	26	3–10
2	26	3–10
3	13	4–13
4	7	6–17
5	2	9–15
Total	74	3–17

To evaluate the inheritance mode of the aggressive periodontitis phenotype, segregation analysis was performed in the 74 families recruited. Pedigrees of the affected individuals were constructed and all the relatives enrolled. We used the SEGREG program of SAGE v.5.4.2 (S. A. G. E. 2008). Mendelian inheritance was assumed to be through an autosomal locus with two alleles A and B, where the A allele was associated with the relevant phenotype. The likelihood for family data (Elston & Stewart 1971) was calculated as a function of the genotype-specific baseline susceptibility parameters (β_{AA}, β_{AB}, β_{BB}), the population allele frequency (q) assuming Hardy–Weinberg equilibrium, and the probability that a parent with each genotype will transmit the allele A (τ_{AA}, τ_{AB}, τ_{BB}). We tested homogeneous no transmission, homogeneous Mendelian transmission, homogeneous general transmission, semi-general transmission and heterogeneous general transmission (S. A. G. E. 2008) assuming the prevalence of aggressive periodontitis in this population as 1% (Tinoco et al. 1997, Susin & Albandar 2005) and no deviations from Hardy–Weinberg equilibrium. Each inheritance mode was tested under the following susceptibility types: two susceptibility loci/factors, two susceptibility loci/factors with dominant or with recessive effects, three susceptibility loci/factors, and three susceptibility loci/factors with decreasing or with increasing effects. The parameters of the model were estimated by the method of maximum likelihood, and provides the overall ln (likelihood), -2ln, and the AIC (Akaike's score) for each model. We used the likelihood ratio test (LRT) to compare each model against a fully general model. Unlike the procedure for usually interpreting p-values, we need to look at p-values that are >0.05 (assuming an α of 0.05). The general model acts as the ''alternative'' hypothesis. In each case, the general model has the most parameters being estimated, whereas the more restrictive model is the nested ''null''. So, for each test, we either ''reject'' the more restrictive model in favor of the general model, if the p-value is <0.05; or, we ''cannot reject'' the more restrictive model (p-value $\geqslant 0.05$). For any given model, the AIC is $-2\ln+2k$, where k is the number of parameters estimated. The model with the lowest AIC was considered to be the most parsimonious among equally likely models.

Results

The segregation analysis results are summarized in Table 3. Compared with the general model, the ''no transmission model'', which indicates no genetics contributions to aggressive periodontitis, was rejected by our segregation analysis ($p = 0.02$ or lower for all tests). The models that incorporated homogeneous or heterogeneous transmissions (the presence of a major gene effect with possible additional polygenic effects) also failed to provide an adequate fit to the data, and these Mendelian models were rejected when compared with the general transmission model ($p = 0.02$ or lower for all tests). The most parsimonious mode of inheritance in each susceptibility type tested was the semi-general transmission mode (τ_{AB} free), particularly in the three susceptibility loci/factors with decreasing effects ($p = 0.31$). This best fit model

Table 3. Parameter estimates and models-fitting from segregation analysis of aggressive periodontitis families

Parameters	Models				
	Homogeneous no transmission With two-susceptibilities	Homogenenous Mendelian With two-susceptibilities	Homogeneous general With two-susceptibilities	Semigeneral transmission With two-susceptibilities	Heterogeneous general With two-susceptibilities
q	1	1	1	1	1
τ(AA)	–	1	1	1	1
τ(AB)	–	0.5	0.5	1	0.5
τ(BB)	–	0	1	0	1
β(AA)	1	1	1	1	1
β(AB)	0	0	0	0	0
β(BB)	0	0	0	0	0
-2LN	− 222.60	− 222.60	− 231.49	− 231.49	− 237.40
LN	111.30	111.30	115.74	115.74	118.70
LRC	14.79	14.79	5.90	5.90	–
p-value	0.02	0.01	0.015	0.05	–
No. parameters estimated	3	3	1	2	–
AIC	− 216.60	− 216.60	− 225.49	− 225.49	− 229.40
	Homogeneous no transmission With two-susceptibilities Dominant	Homogeneous Mendelian With two-susceptibilities Dominant	Homogeneous general With two-susceptibilities Dominant	Semigeneral transmission With two-susceptibilities Dominant	Heterogeneous general With two-susceptibilities Dominant
q	1	1	1	1	1
τ(AA)	–	1	1	1	1
τ(AB)	–	0.5	0.5	1	0.5
τ(BB)	–	0	1	0	1
β(AA)	1	1	1	1	1
β(AB)	0	0	0	0	0
β(BB)	0	0	0	0	0
− 2LN	− 222.60	− 222.60	− 231.49	− 231.49	− 237.40
LN	111.30	111.30	115.74	115.74	118.70
LRC	14.79	14.79	5.90	5.90	–
p-value	0.002	0.001	0.015	0.052	–
No. parameters estimated	3	3	1	2	–
AIC	− 216.60	− 216.60	− 225.49	− 225.49	− 229.40
	Homogeneous no transmission With two-susceptibilities Recessive	Homogeneous Mendelian With two-susceptibilities Recessive	Homogeneous general With two-susceptibilities Recessive	Semigeneral transmission With two-susceptibilities Recessive	Heterogeneous general With two-susceptibilities Recessive
q	1	1	1	1	1
τ(AA)	–	1	0.91	1	1
τ(AB)	–	0.5	1	0.92	0.92
τ(BB)	–	0	0.60	0	0
β(AA)	1	1	1	1	1
β(AB)	0	0	0	0	0
β(BB)	0	0	0	0	0
− 2LN	− 75.65	− 258.76	− 303.70	− 332.65	− 337.55
LN	37.82	129.38	151.85	166.32	168.77
LRC	261.8	78.78	33.84	4.90	–
p-value	0.0001	0.0001	0.0001	0.086	–
No. parameters estimated	3	3	1	2	–
AIC	− 69.65	− 252.76	− 293.70	− 324.65	− 329.55
	Homogeneous no transmission With three-susceptibilities	Homogeneous Mendelian With three-susceptibilities	Homogeneous General With three-susceptibilities	Semigeneral transmission With three-susceptibilities	Heterogeneous general With three-susceptibilities
q	1	1	1	1	1
τ(AA)	–	1	1	1	1
τ(AB)	–	0.5	0.5	1	1
τ(BB)	–	0	0.99	0	0

Table 3. (Contd.)

	Homogeneous no transmission With three-susceptibilities	Homogeneous Mendelian With three-susceptibilities	Homogeneous General With three-susceptibilities	Semigeneral transmission With three-susceptibilities	Heterogeneous general With three-susceptibilities
β(AA)	1	1	1	1	1
β(AB)	0	0	0	0	0
β(BB)	0	0	0	0	0
− 2LN	− 226.49	− 237.83	− 244.10	− 248.98	− 254.68
LN	113.24	118.91	122.05	124.49	127.34
LRC	28.19	16.85	10.58	5.70	–
p-value	0.0001	0.0001	0.001	0.058	–
No. parameters estimated	3	3	1	2	–
AIC	− 218.49	− 229.83	− 234.10	− 240.98	− 246.68
	Homogeneous no transmission With three-susceptibilities Decreasing	Homogeneous Mendelian With three-susceptibilities Decreasing	Homogeneous general With three-susceptibilities Decreasing	Semigeneral transmission With three-susceptibilities Decreasing	Heterogeneous general With three-susceptibilities Decreasing
q	0	0	0	0	0
τ(AA)	–	1	0.20	1	1
τ(AB)	–	0.5	0	0	0
τ(BB)	–	0	0.17	0	0
β(AA)	0	0	0	0	0
β(AB)	0	0	0	0	0
β(BB)	1	1	1	1	1
− 2LN	− 131.20	− 252.53	− 226.81	− 336.49	− 338.79
LN	65.60	126.26	113.40	168.24	169.38
LRC	207.5	86.26	111.9	2.303	–
p-value	0.0001	0.0001	0.0001	0.31	–
No. parameters estimated	3	3	1	2	–
AIC	-123.20	-244.53	-214.81	-328.49	-330.79
	Homogeneous no transmission With three-susceptibilities Increasing	Homogeneous Mendelian With three-susceptibilities Increasing	Homogeneous general With three-susceptibilities Increasing	Semigeneral transmission With three-susceptibilities Increasing	Heterogeneous general With three-susceptibilities Increasing
q	1	1	1	1	1
τ(AA)	–	1	1	1	1
τ(AB)	–	0.5	0.5	1	1
τ(BB)	–	0	0.42	0	0
β(AA)	1	1	1	1	1
β(AB)	0	0	0	0	0
β(BB)	0	0	0	0	0
− 2LN	− 222.24	− 591.32	− 242.59	− 874.01	− 878.88
LN	111.12	295.66	121.29	437.00	439.44
LRC	656.6	287.5	636.2	4.87	–
p-value	0.0001	0.0001	0.0001	0.087	–
No. parameters estimated	3	3	1	2	–
AIC	− 214.24	− 583.32	− 232.59	− 866.01	− 870.88

The models ''homogeneous no transmission'', ''homogeneous Mendelian'', ''homogeneous general'', and ''semigeneral'' are always compared to the ''heterogeneous general'' model (last column). Also, assumptions such as the effect of susceptibility alleles is dominant, recessive, decreases from one allele to the other, or increases from one allele to the other are included. The model with the lowest AIC and with a *p*-value >0.05 is the best-fitting model for the data. In these results, the semigeneral model was always the best-fitting model.

q, gene frequency; τ(AA), τ(AB), τ(BB), transmission probabilities; β(AA), β(AB), β(BB), baseline parameters for types AA, AB, BB;-2LN, log likelihood; LN, likelihood; LRC, likelihood ratio criterion; AIC, Akaike's score.

allows the heterozygote transmission probability to vary (i.e. suggests an excess of risk alleles being transmitted from heterozygous parents.

Discussion

The current understanding of the pathogenesis of periodontal diseases suggests that they occur as a result of complex interactions between periodontopathic microorganisms and host factors. The aetiology, although unclear, includes the

sum of environmental and genetic factors, which can result in variations in inflammatory or immunological processes (Diehl et al. 2003). For these reasons, periodontitis is considered as a complex disease whose phenotype is determined by both the genetic trait as well as the environmental influences on the affected individual (Yoshie et al. 2007). These types of complex traits pose special challenges for genetic analysis because of gene–gene and gene–environment interactions, genetic heterogeneity, low penetrance and limited statistical power (Glazier et al. 2002).

Aggressive periodontitis shows strong familial aggregation which suggests the presence of a genetic component (Van der Velden et al. 1993, Tinoco et al. 1998). Previous segregation analyses of families with aggressive periodontitis support a major locus hypothesis and potential inheritance models include autosomal dominant (Boughman et al. 1986, Marazita et al. 1994), autosomal recessive (Long et al. 1987) and X-linked dominant (Hart et al. 1992).

Our results confirm our hypothesis that genetic factors play a role in aggressive periodontitis and we were able to rule out the ''no transmission'' model in our segregation analysis. The best fit model in our data was the model that allows the heterozygote transmission probability to vary, called the semi-general transmission model (τ_{AB} free). The usual interpretation for this kind of result is that there is evidence of transmission; however, the transmission is not of a straightforward single Mendelian gene. We can also rule out a large number of small gene effects. Therefore, the best explanation is a few major loci contributing to aggressive periodontitis, with or without some interactions with environment factors.

Our study has obvious limitations. Out of the 475 individuals included in the analysis, 40 were younger than 15 years of age. One can argue that a subset of these children could develop aggressive periodontitis at a later age, and if they were included in the analysis our results could have been different. To address this concern, we have also analysed our data including age of onset at 15 years of age as a variable. The results of this data manipulation did not substantially change the results reported here (data not shown). Another limitation is the possibility that localized and generalized diseases are distinct entities. The difference between localized and generalized aggressive periodontitis is in the number and type of teeth involved, and the two diseases will progress similarly. Furthermore, around 35% of originally classified localized disease will progress to generalized disease (Brown et al. 1996). Also, among the 74 families studied, 13 families have only cases of localized disease and 42 families have only cases with generalized disease. The remaining 19 families had ''mixed'' families, with cases of incipient, localized and generalized disease (Table 4). These data can be used to support the hypothesis that generalized and localized disease may be caused by distinct genetic factors but there is obvious overlap as evidenced from the presence of ''mixed'' families. In addition, these data do not necessarily preclude our assumption that a similar inheritance mode is operating for both localized and generalized diseases. Future approaches should investigate more discreet groups (only localized disease families, only generalized disease families, and ''mixed'' families) when sample sizes permit. Finally, an inherited difficulty of genetic studies of periodontitis is the disease modification by environmental factors. In some families with relatively older members, one could argue that aggressive periodontitis could be mimicked in individuals who have advanced chronic periodontitis due to extremely poor oral hygiene coupled with other risk factors such as smoking or co-existing morbidities like diabetes. To minimize this risk, individuals with these environmental confounders were not included as affected in the analysis.

Table 4. Distribution of aggressive periodontitis phenotype among probands and relatives per family

Number of families	Incipient aggressive periodontitis	Localized aggressive periodontitis	Generalized aggressive periodontitis
9	X	X	X
1	X	X	
6		X	X
3	X		X
0	X		
13		X	
42			X
74			

The statistical genetic evidence we are presenting here supports a few major loci involvement in aggressive periodontitis and family linkage studies can be used to search for the genes contributing to aggressive periodontitis. Previously, only three family linkage studies have been performed on families with aggressive periodontitis (Boughman et al. 1986, Hart et al. 1993, Li et al. 2004). The first two studies suggested that a locus responsible for aggressive periodontitis was located on chromosome 4, while the last study reported evidence of linkage on chromosome 1q25. In addition, mutations were described in the *cathepsin C* gene, the gene defective in the allelic syndromes Papillon-Lefèvre and Haim-Munk (Hart et al. 2000a), in aggressive periodontitis families (Hart et al. 2000b, Noack et al. 2004, 2008a, b). The aggressive periodontitis in these particular families is autosomal recessive, and the results of the segregation analysis presented here suggest that families segregating *cathepsin C* mutations (phenocopies of aggressive periodontitis) are probably not frequent among the 74 families studied.

In summary, our segregation analysis supports a semi-general transmission model (τ_{AB} free) for aggressive periodontitis. Thus, it is more likely that a few loci with small effects contribute to aggressive periodontitis, with possibly the influence of environmental factors.

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Clinical Relevance

Scientific rationale for the study: Understanding the mode of inheritance of aggressive periodontitis can better guide future molecular studies aiming to identify contributing genetic factors to the condition.

Principal findings: Our results provide strong support for the hypothesis that genetic factors play a role in aggressive periodontitis, under a model of variable heterozygote transmission.

Practical implications: Family-based designs provide the opportunity to study variation in the phenotype and provide evidence that justifies future family-based genetic analysis. From these approaches comes the possibility to localize disease loci through linkage analysis. The identification of the genetic variation leading to aggressive periodontitis can improve individual risk assessments of this condition in the future.