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Genetic Analysis of Juvenile Periodontitis in Families Ascertained through an Affected Proband

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SUMMARY

Data from 28 families ascertained through a proband with juvenile periodontitis were used to test a series of Mendelian models of inheritance that included both autosomal and X-linked transmission. There was strong evidence of familial aggregation of this progressive dental disease, and the best-fitting model was an autosomal recessive model. Because of the rather limited age range for expression of the disease in this situation, simulations were done, in a model-choice analysis using samples of this size, to assess the chance of mistaking an autosomal dominant disease (with masking of the affected phenotype outside a specified age range) for an autosomal recessive disease. While the rate of Type II error was fairly high (40%) when competing models in these simulations were compared, these data suggest that it is reasonable to infer that juvenile periodontitis is an autosomal recessive disorder.

INTRODUCTION

Juvenile periodontitis (JP) is a progressive dental disease marked by loss of periodontal support for selected teeth and is clincally identified by loss of attachment around teeth in adolescents or young adults. Although in both etiology and clinical progression juvenile periodontitis is clearly different from the ubiquitous, chronic adult form of periodontitis, there is still some debate as to whether localized JP (typically involving only the molars and incisors) has an etiology separate from the rapidly progressive periodontitis characterized by

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more generalized occurrence of gingival pockets about all teeth and subsequent loss of attachment. Long et al. (1986) reported the occurrence of both the localized and the rapidly progressive forms of JP in the same family and argued for a common etiology.

The prevalence of JP, in either form, is still a question of some debate, and to date there have been few good population surveys capable of producing reliable estimates. A survey of 650 children and young adults among Pima Indians showed that the occurrence of all periodontal disease increased with age, rising from 0.4% in 10–14-year-olds to 12.8% in 20–24-year-olds (Schlossman et al. 1986).

There is clear familial aggregation in JP, which has prompted a number of researchers to propose a possible genetic mechanism for it. On the basis of analysis of 129 first-degree relatives of 31 JP probands, Saxen (1980) proposed an autosomal recessive model of inheritance for JP. Saxen and Nevanlinna (1984) reported on 30 families, ascertained through probands with JP, in which there were no affected parents and nine affected siblings (of 52 examined) and concluded that JP may be an autosomal recessive disease. Melnick et al. (1976), however, suggested that the clear excess of affected females may be due to an X-linked dominant form of JP with somewhat reduced penetrance in the heterozygous female. Long et al. (1986) analyzed 33 families ascertained through a proband with JP and found the autosomal recessive model to be the model of choice when these two Mendelian models were examined.

JP presents an interesting range of problems for genetic analysis. The disease has a variable age of onset with both upper and lower limits for phenotypic expression. It usually cannot be diagnosed before the age of 12. On the other hand, loss of periodontal attachment in adults >35 years of age may represent the chronic form of adult periodontal disease, limiting the ability to make accurate diagnoses in many adults. Furthermore, it is very difficult to obtain accurate clinical histories on edentulous adults to establish the cause of their loss of teeth, and therefore many older individuals in earlier generations may be classified as unknown or nonaffected for the JP phenotype when indeed they had some form of the disease in the past. This means that only individuals within a limited age range can be reliably diagnosed as affected. Thus, phenotypic information available for pedigree studies is generally truncated for both the oldest and youngest generations.

Here we present an analysis of 28 pedigrees, ascertained through probands with JP, in which a series of Mendelian models were evaluated to discriminate between competing models proposed by others. A nongenetic sporadic model, both autosomal and X-linked single-locus models, as well as a generalized single-locus model with sex-specific transmission, were examined in an attempt to test which Mendelian model best explains these data. In addition, these 28 pedigree structures were used in a simulation analysis to determine whether the presence of strict upper and lower age limits on the expression of a Mendelian disease (a significant problem presented by this disease) could lead to the choice of a wrong model of inheritance for samples of this size.

METHODS

Pedigree Data

Twenty-eight families were ascertained through probands diagnosed with JP. The probands were seen at either the University of Maryland Dental School or The Johns Hopkins Hospital and were diagnosed as having JP if the proband was <26 years of age and had loss of attachment of >5 mm around at least three teeth (two of which must be first molars). Family histories were obtained by interview, with documentation of edentulous and adult-periodontitis phenotypes among relatives of the proband. Relatives were invited to participate and were offered a similar dental exam. All clinical examinations were performed by one of us (J.B.S.), and standard techniques for measuring clinical indices were employed. Individuals >35 years of age who had pockets >5 mm around two or more (but less than 16) teeth were classified as having adult periodontitis.

Among the 372 individuals in these 28 families, 62 individuals were diagnosed as having JP, whereas 95 individuals were examined and diagnosed as unaffected (47 of these 95 were diagnosed as having adult periodontitis, however). A total of 215 of the 372 individuals in these pedigrees had unknown phenotypes with regard to JP either because they were unavailable or were too young for examination. Figure 1 shows the distribution of ages for all individuals, noting their phenotypic status (unknown, affected, or normal). As would be expected, those affected with JP (including one individual with periodontitis of deciduous dentition) are clustered in the younger ages, with normal individuals spread more uniformly across age groups. The median age for the 62 individuals diagnosed with JP was 20 years, and that for the 95 normal individuals was 25 years.

A series of models of inheritance was evaluated on these families using the pedigree analysis package (PAP) with an approximate correction for ascertainment through an affected proband (Hasstedt and Cartwright 1981). This approximate correction involves conditioning the log-likelihood of the model evaluated on the entire pedigree by subtracting the log-likelihood of observing an affected proband, and it is valid for situations in which the probability of ascertainment is low (Cannings and Thompson 1977; Thompson 1981).

With this approach, comparisons between different models in a hierarchical series can be made under the likelihood-ratio criterion in which minus twice the difference in log-likelihoods between a reduced model and a more general model is treated as an approximate χ^2-statistic with degrees of freedom equal to the difference in the number of parameters estimated. On small samples, however, the conditional likelihood function frequently maximizes at a boundary, invalidating this test statistic.

Simulations

To assess the impact of a truncation of the JP phenotype at both young and old ages, a simulation study was carried out using these 28 pedigree structures.

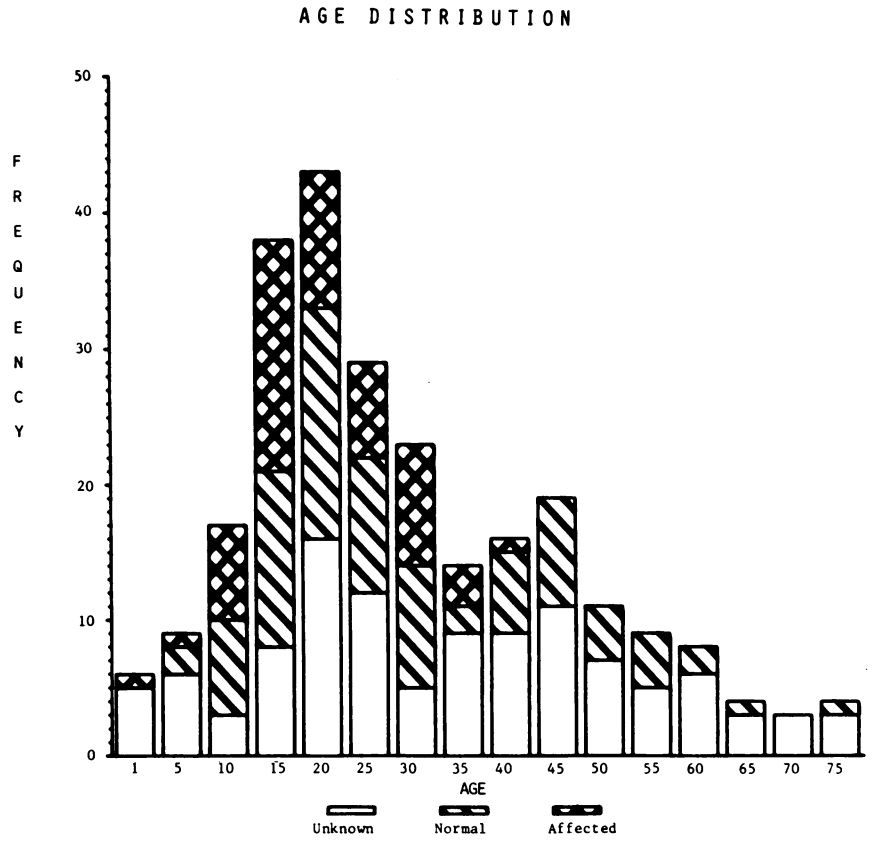

FIG. 1.—Age distribution of 372 members of 28 pedigrees ascertained through probands with JP.

By means of the techniques described by Beaty and Boughman (1986), affected and normal phenotypes were simulated for all members of these 28 pedigrees. Since the goal of this analysis was to see whether an autosomal dominant disease would be mistakenly identified as recessive if there were strict age limits on the expression of the disease, an autosomal dominant model of inheritance was used to assign phenotypes. The frequency for the disease allele was set to .03, which corresponds to the prevalence predicted by the best-fitting Mendelian model. By changing the affected phenotype to an unknown phenotype before analysis, complete masking of the disease phenotype was imposed in all individuals who were either <10 years of age or >35 years of age. The log-likelihood of a simple autosomal dominant model (with allele frequency set to .03) and the log-likelihood of a simple autosomal recessive model (with allele frequency set to .242 to correspond to this same prevalence) were then computed for each of 100 replicates of this set of 28 pedigrees. Comparison between these two competing models was done by simple model choice; that is, the model with the highest relative probability was chosen as the best-fitting

model. Although this analysis did not involve any estimation of parameters as done on the real data, it serves as an indication of how often the wrong genetic model would be chosen solely because of an age limitation on the expression of the disease phenotype. Misclassification of an autosomal dominant pedigree as supporting an autosomal recessive model—i.e., acceptance of the wrong model—can be thought of as a Type II error, although it is not directly equivalent to statistical power in the classic Neyman-Pearson sense.

RESULTS

The series of models examined on these 28 families included a sporadic model, which presumed that all individuals had the same genotype and estimated the probability of being affected with the JP phenotype separately for males and females. For convenience, the transmission parameters listed in table 1 are kept at their autosomal expectations; but since this model only allows one genotype, these parameters do not enter into the likelihood equation. In effect, this sporadic model states that the causes of JP are nongenetic and that relatives are independent of one another with respect to risk. The first row of table 1 shows the estimated probabilities of being affected under this sporadic model, and these values can be thought of as an estimated prevalence of JP among all nonproband family members conditioned on ascertainment. Females have a slightly higher estimated risk than do males (28.17% vs. 22.81%), a result that also has been reported by other workers. These estimates reflect the higher number of affected nonproband females (27% or 16 of 60) compared with nonproband males (23% or 18 of 79) seen in these families.

A general autosomal Mendelian model was examined on these families in which the probability of being affected for homozygous normal individuals (here genotype 3) was assumed to be .0, that for homozygous affected individuals was assumed to be 1.0, and the probability of a heterozygote was estimated along with the frequency of the putative JP allele. If the disease were truly recessive, this parameter should be .0; if it were truly dominant, this parameter should be 1.0. As seen in table 1, both males and females had very low estimated values for this parameter. The strong familial aggregation in JP is evidenced by the improvement in the ln-likelihood of this Mendelian model, which can be used to reject the null hypothesis that $P = 1.0$ (i.e., can be used to reject the sporadic model) by computing a χ^2-test statistic—i.e., $\chi^2 = -2(-72.735 + 65.016) = 15.42$ with 1 df, $P < .001$. A strictly recessive model was also examined and was not significantly different from this more general autosomal model, suggesting that the simple autosomal recessive model is the most parsimonious explanation for these data. A number of other autosomal models that attempted to estimate the probability of the two homozygotes being affected were examined. However, the likelihoods of these general models consistently maximized at the upper or lower boundary for penetrance in genotypes 1 and 3, respectively.

The increased risk in females has prompted some workers to postulate an X-linked dominant model of inheritance for JP, a model that would lead to almost a 2:1 excess of affected females for a rare disease allele. To examine this

TABLE 1

RESULTS OF EVALUATING A SERIES OF MODELS OF INHERITANCE ON 28 FAMILIES ASCERTAINED THROUGH PROBANDS WITH JP

MODEL	LN-LIKELIHOOD	ALLELE FREQUENCY	P(affected|genotype 1)		P(affected|genotype 2)		P(affected|genotype 3)		P(male genotype 2 → mutant allele)	
			Male	Female	Male	Female	Male	Female	Son	Daughter
Sporadic	−72.735	1.0	.2281 (.0557)	.2817 (.0535)	=	=	=	=	.5	.5
General autosomal	−65.016	.2343 (.0777)	1.0	1.0	.0218 (.0746)	.0923 (.1036)	.0	.0	.5	.5
Autosomal recessive ..	−66.155	.2420 (.0571)	1.0	1.0	.0	.0	.0	.0	.5	.5
General X-linked	−68.322	.4283 (.1864)	...	.6147 (.2132)	.3474 (.1121)	.0315 (.0799)	.0160 (.1137)	.0	.0	1.0
X-Linked dominant ...	−77.050	.1039 (.0498)	...	1.0	1.0	.3584 (.0915)	.0	.0	.0	1.0
General single-locus ..	−65.003[a]	.3549	1.0	.8585	.0139	.0247	.0003	.0519	.035	1.01[a]

NOTE.—Values in parentheses are ±SE.

[a] Maximized at boundary.

possibility, an X-linked model with arbitrary penetrance in heterozygous females was also examined, as shown in the fifth row of table 1. Here an estimated 35.8% of heterozygous females were affected, whereas by design this model stated that 100% of males carrying the mutant X-linked allele would be affected and 0% of males with the normal allele on their X chromosome would be affected. Aside from these penetrance parameters, this X-linked model specifies that a male of genotype 2 (equivalent to a hemizygous male carrying the mutant allele) has probability .0 of transmitting this allele to a son and probability 1.0 of transmitting this to a daughter (see the last two cols. of table 1). This is the key difference between an autosomal model (in which both of these segregation probabilities are .5) and any X-linked model. As seen in table 1, the ln-likelihood of this X-linked dominant model is much lower than that for the autosomal model—and is even lower than that of the sporadic model that involved fitting the same number of parameters.

Also shown in table 1 is a more general X-linked, single-locus model, in which the penetrance in both homozygous and heterozygous females (genotypes 1 and 2) was estimated, along with the penetrance in both possible male genotypes. Here females homozygous for the putative X-linked JP allele had a 61.5% chance of displaying the affected phenotype, whereas heterozygous females had a very low probability of displaying the trait. Males hemizygous for this putative allele had an estimated 35% probability of being affected, whereas males with the normal allele on their X chromosome were effectively risk free. This general X-linked model is, in essence, a recessive model with incomplete penetrance even in homozygous females—and had a much higher ln-likelihood than did the X-linked dominant model. Note, however, that this best-fitting X-linked model was still not as likely as the autosomal recessive model.

Rigorous comparisons between these two models must involve comparing each separately to a more general single-locus model with sex-specific segregation probabilities. To accomplish this, a general model of inheritance was examined in which the allele frequency was estimated, along with the penetrance in the second genotype (separately for males and females) and the two segregation parameters specifying the probability of a male transmitting the mutant allele to sons and daughters, respectively. When this general model was evaluated on these data, the likelihood function maximized on the upper boundary for the father-daughter transmission parameter, invalidating any direct computation of test statistics and making it impossible to compute SEs for the final estimators. It is worth noting, however, that the ln-likelihood at this maximum value for the general model was not substantially greater than that for the autosomal model and would not permit rejection of the null hypothesis that the segregation probabilities are indeed .5 for both male and female offspring.

To investigate the consequences of this truncation of expression of the JP phenotype for these 28 pedigrees, we simulated 100 replicates of an autosomal dominant disease with complete truncation of the affected phenotype at <10 and >35 years of age. These simulated phenotypes were then used to compute the likelihood of both an autosomal dominant model and an autosomal recessive model (in which the respective allele frequencies for these two models

were set to reflect a prevalence of .059). Comparing the two log-likelihoods of a simple autosomal dominant and a simple recessive model over the 100 replicates of the simulated dominant data showed that the correct model was chosen 60 of 100 times. Although this rate of Type II error is high, it suggests that an autosomal dominant mechanism is unlikely to be the true mechanism for JP in these data.

DISCUSSION

JP is a relatively rare dental disease that shows significant familial aggregation and has prompted several investigators to postulate a genetic mechanism for it. Although Melnick et al. (1976) suggested that the excess of affected females seen in 19 sibships could be due to an X-linked dominant mechanism, others have favored an autosomal recessive model of inheritance for this disease (Saxen and Nevanlinna 1984; Long et al. 1986).

Analysis of these 28 pedigrees strongly suggests an autosomal recessive model of inheritance for JP. The simple autosomal recessive model was not significantly different from a more general autosomal model and was more likely than either X-linked models examined here. Of the 31 parents of probands with phenotypic information (25 had unknown phenotypes), only two were identified as affected with JP. However, other parents were not entirely free of dental disease: 11 were reported to have adult periodontitis, 14 were edentulous (11 of these had no information on periodontal history), and only 4 had a normal phenotype. This ambiguity in classifying individuals illustrates part of the difficulty in conducting family studies of dental diseases such as JP.

In these families, 19 (68%) of the 28 probands were female and 37 (60%) of 62 affected nonprobands were female. This apparent excess of females affected with JP may reflect a bias in ascertainment, since (1) females may be more likely to be diagnosed with JP compared with males or (2) there may be a true difference between the sexes in the expression of the underlying disorder. Such an excess of females was cited by Melnick et al. (1976) as evidence for an X-linked dominant mode of inheritance, and Baer and Benjamin (1974) noted a tendency for JP to follow maternal lines in half sibships. However, the analysis presented here provides little evidence that any putative JP gene is actually on the X chromosome. Although the estimated transmission parameters from father to son and from father to daughter for a general single-locus model shown in table 1 appear compatible with an X-linked model, the likelihood of this general model was not appreciably greater than that for a comparable autosomal model.

JP is routinely diagnosed using clinical indices measuring loss of gingival attachment. However, defects in neutrophil chemotaxis have been reported in periodontal disease (Cianciola et al. 1977), and 86% of JP patients in a recent study (Suzuki et al. 1984) showed such chemotactic defects. This chemotactic defect has been found in some relatives of JP patients (Vandesteen et al. 1984; Van Dyke et al. 1985), but it has not yet been shown that this neutrophil abnormality is either a necessary or a sufficient condition for the development of clinical JP. Some investigators support the definition of JP as an infectious disease requiring the presence of certain periodontal pathogens (e.g.,

Hemophilus actinomycetumcomitans) that have been associated with JP (Slots et al. 1982; Vincent et al. 1985). Although these pathogens could be shared among relatives, there is little evidence that they alone can account for the observed patterns of familial aggregation of the disease.

Currently accepted clinical definitions of JP impose certain limitations on identifying affected individuals, since the disease is intrinsically age limited. Children without permanent dentition can rarely be diagnosed as affected, although periodontitis of deciduous teeth has been observed. Since the eruption of permanent molars can occur as late as 12 years of age, it is often impossible to identify the JP phenotype in younger individuals. Possibly more important, however, is the difficulty in identifying the affected phenotype in older individuals. It is frequently difficult to establish the cause of tooth loss for adults who are edentulous at examination—and JP itself generally results in tooth loss. Since the adult form of periodontitis is so common, adults >35 years of age with some form of periodontal disease are likely to be misdiagnosed as unaffected for JP when, indeed, they may have a mild form of the disease. There is a wide range of pathogenetic expression of this disease, and it is probably heterogeneous. Thus, many affected adults may be (1) misclassified as unaffected with JP or (2) simply classified as unknown.

This truncation in phenotypic expression could result in a dominant form of disease appearing to be recessive, because only sibs will appear as affected (since their parents and their own children may be outside the age range traditionally associated with JP and will be frequently misclassified as unknown or nonaffected). To approach the question of how often an autosomal dominant disease could be mistaken for a recessive disease, we simulated phenotypes for these 28 pedigrees and compared the ln-likelihoods of these two competing models over 100 replicates in a model-choice approach. This analysis showed that 60% of these autosomal dominant data were correctly identified even in the presence of a strict age limitation on the expression of the disease. Although this model-choice approach cannot estimate true statistical power of a hypothesis-testing situation, it is reassuring that there would be only a moderate chance of misclassifying a dominant disease as recessive even in the presence of a very strict age limit on expression of the disease.

In future studies of diseases such as JP it will be most important to obtain accurate dental histories to establish as accurately as possible the clinical phenotype for all age groups. Preferable to this, however, would be to obtain a biochemical or cellular marker for the underlying pathological process involved in this disease. As family studies are expanded, inclusion of comprehensive information on studies of neutrophil chemotaxis and the presence of specific periodontal pathogens is essential. With clarification of observed associations between these abnormalities and the clinical disease JP, our understanding of both the etiology and the pathogenetic process of JP will improve.

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