Genetic causes involved in *Leishmania Chagasi* infection innortheastern - Brazil
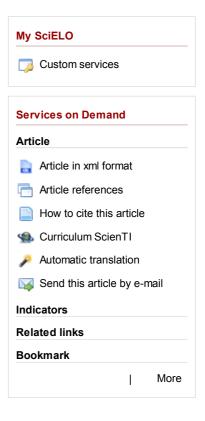
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ABSTRACT

A sample of 502 individuals from 94 families from Jacobina, State of Bahia, Brazil, was investigated to determine the causal mechanisms involved in *Leishmania chagasi* (the causal agent of visceral leishmaniasis in the American hemisphere) infection, as measured by the intradermic reaction to antigens derived from this parasite, using complex segregation analyses. The results showed evidence of a major genetic mechanism acting on infection, with a frequency of a recessive (or additive) susceptibility gene (q) of approximately 0.45. A small multifactorial component (H = 0.29) acting in conjunction with a major recessive gene (q = 0.37) is not ruled out as a concomitant causative factor.

INTRODUCTION

Variation in host resistance/susceptibility to infection by intracellular parasites has been demonstrated to be genetically controlled in experimental animals (cf. Skamene and Pietrangieli, 1991; Skamene, 1998). Innate susceptibility to *Leishmania donovani* infection in mice is controlled by a single autosomal gene (*Lsh*) segregating for incompletely dominant resistant and recessive susceptible alleles (Bradley, 1977), located on chromosome 1 (Bradley *et al.*, 1979). Acquired resistance is influenced by genes linked to the major (H-2) and minor (H-11) histocompatibility complexes (Blackwell *et al.*, 1980, 1985; Roberts *et al.*, 1989a,b). Experimental infections in mice have demonstrated that gene(s), also on chromosome 1, regulate resistance/susceptibility to *Salmonella typhimurium* (= *Ity*) (Plant and Glynn, 1974, 1976), *Mycobacterium bovis* (= *Bcg*) (Gros *et al.*,

1981; Skamene *et al.*, 1982), *M. lepraemurium* (Brown *et al.*, 1982; Skamene *et al.*, 1984) and *M. intracellulare* (Goto *et al.*, 1984). Studies carried out with three phylogenetically distinct groups of microorganisms provided evidence that the *Bcg/Ity/Lsh* gene regulates some key point in the pathway to priming/activation of macrophages for antimicrobial activity (cf. Blackwell, 1989; Blackwell *et al.*, 1991; Schurr *et al.*, 1991a,b). A gene encoding a phagocyte membrane protein (Nramp1) was shown to be allelic to the *Bcg/Ity/Lsh* complex (Govoni *et al.*, 1996).

Recent studies, utilizing high resolution genetic mapping techniques, have revealed that an array of closely linked marker genes has been conserved between murine chromosome 1 and the telomeric end of the long arm of human chromosome 2 (Schurr *et al.*, 1989, 1990; Mock *et al.*, 1990; Malo *et al.*, 1991; Barton *et al.*, 1992). Nevertheless, other studies (Blackwell, 1992, 1998; Shaw *et al.*, 1993; Levee *et al.*, 1994) could not provide conclusive evidence of linkage between a putative "leprosy", "visceral leishmaniasis" or "tuberculosis" gene and DNA markers on the 2q35 chromosomic region (Morgan *et al.*, 1994), which is believed to have homology to mouse chromosome 1 (Vidal *et al.,* 1993).

In humans, segregation analysis studies on leprosy and tuberculosis have shown conflicting results. While some indicated the presence of a clear genetic mechanism (Smith, 1979; Demenais *et al.*, 1985; Haile *et al.*, 1985; Abel and Demenais, 1988; Wagener *et al.*, 1988; Abel *et al.*, 1995), other studies were unable to establish evidence of a major genetic component (Serjeantson *et al.*, 1979; Shields *et al.*, 1987; Feitosa *et al.*, 1995). For a recent review, see Blackwell (1996).

The aim of the present study was to investigate possible genetic mechanisms acting on resistance/susceptibility to *Leishmania chagasi* (the causal parasite of visceral leishmaniasis in the American continent) infection in a sample of families from Jacobina, Brazil, using complex segregation analysis.

MATERIAL AND METHODS

The data were collected at random from a population living in an area endemic for visceral leishmaniasis, and consisted of nuclear families residing in Jacobina, Bahia State, Brazil (cf. Cabello *et al.*, 1995; Lima *et al.*, 1996). The total sample comprised 1,604 individuals belonging to 243 nuclear families, of which 502 individuals were tested for *Leishmania* infection. A skin test was used to characterize *Leishmania* infection. An intradermal injection was made of 50 ㎎ of soluble protein from freeze-thaw preparations of *L. chagasi* centrifuged at 35,000 *g.* Skin tests were considered positive if the diameter of the reaction was larger than 5 mm, approximately two days after inoculation (Reed *et al*., 1986).

Segregation analysis

Segregation analyses were done on the 502 individuals, belonging to 94 nuclear families (Table I). This analysis was performed using the unified model (Lalouel *et al.*, 1983), from the computer program POINTER (Lalouel and Morton, 1981; Morton *et al.*, 1983), which incorporates the transmission frequencies (Elston and Stweart, 1971) into the mixed model (Morton and MacLean, 1974). The mixed model assumes an underlying liability scale to which a major locus, multifactorial component, and random environment contribute independently. The major gene effect results from segregation at a single locus with two alleles (*A*, *a*), where genotypes are distributed according to Hardy-Weinberg proportions. The estimated parameters are: the frequency (**q**) of the allele *a* responsible for the infection; the displacement between the two homozygous means (**t**); position of the mean of the heterozygote relative to the means of the two homozygous genotypes (**d**), and two parameters representing the multifactorial heritabilities in children (**H**) and parents (**HZ**). Additional parameters, t_{AA}, t_{Aa}, t_{aa}, can be estimated to test deviations from Mendelian transmission of the major effect from parent to offspring, and denote the probabilities of transmitting allele **A** for genotypes **AA**, **Aa**, and **aa**, respectively. Under Mendelian transmission, $t_{AA} = 1$, $t_{Aa} = 1/2$, $t_{aa} = 0$, while no major gene transmission is obtained when the tree taus are equal.

Table I - Distribution of studied families, according to family size, from Jacobina, Bahia State, Brazil.

Family size	Number of families
1	3
2	2

3	14
4	17
5	17
6	17
7	10
8	6
9	5
11	1
12	2

In order to infer a major locus acting together or not with a polygenic mechanism, three conditions are usually required: i) rejection of the hypothesis: $d = t = q = 0$ (no major effect); ii) no rejection of Mendelian transmission (when $t_{AA} = 1$, $t_{Aa} = 1/2$, $t_{aa} = 0$), and iii) rejection of the no Mendelian transmission model (when $t_{AA} = t_{Aa} = t_{aa}$). Different hypotheses were tested by estimating or fixing parameters of the complete model. Standard tests of hypotheses were performed using the likelihood ratio criterion (**-2lnL**). Alternatively, the Akaike Information Criterion (**AIC**) (Akaike, 1974) was used to compare the likelihood of nonnested models. **AIC** is defined as **-2lnL** plus twice the number of estimated parameters, and the lowest **AIC** value is considered to be the best model.

Stepwise multiple regression was applied in order to detect concomitant variation that could confound genetic effects on infection. The independent variables used in the model were: cubic polynomial on age, sex and the interactions between them. Restricting to terms significant at the 5% level, only age in years showed a significant effect, according to the equation: $Y = 0.141348 + 0.0073$ (age); $F_{(1,500)} = 32.88$. Thus, the segregation analysis was carried out using liability class values provided by this regression analysis (Table II).

Table II - Liability values to *Leishmania chagasi* infection according to specific age groups (in years).

Age groups	Liability classes
0-50	0.1596
6-10	0.1961
11-15	0.2326

16-20	0.2691
21-25	0.3056
26-30	0.3421
31-35	0.3786
36-40	0.4151
> 40	0.4698

RESULTS

Segregation analysis of *Leishmania* infection was applied to the sample of 502 individuals in 94 nuclear families. The degree of dominance reached value zero for the Mendelian mixed model (Table III), suggesting a recessive gene effect (model 2 vs. model 1: $c^2_1 = 318.50 - 318.44 = 0.06$, P = 0.806). Compared with the Mendelian mixed model (d = 0), the model ignoring familial resemblance and the model of no major gene were both rejected (model 4 vs. model 2: $c^2_3 = 356.45 - 318.50 = 37.95$, P < .001; model 3 vs. model 2: $c^2_2 = 324.67 - 318.50 = 6.17$, P = 0.046, respectively). A multifactorial component in addition to the major gene was not necessary to explain familial aggregation (model 5 vs. model 1: $c^2_1 = 320.58 - 318.44 = 2.14$, P = 0.144). Nevertheless, in addition to a major gene, a small multifactorial cause (H = 0.29) is suggested, when the AIC criterion is utilized. The data were compatible with a recessive or an additive mode of inheritance (model 6 vs. model 5: $c^2_1 = 322.84 - 320.58 = 2.26$, P = 0.133; model 7 vs. model 5: $c^2_1 = 322.17 - 320.58 = 1.59$; P = 0.207, respectively), while a dominant model was rejected (model 8 vs. model 5: $c^2_1 = 327.81 - 320.58 = 7.23$; P = 0.007). A model that allows estimation of taus does not differ significantly from the mixed model with fixed Mendelian transmission probabilities ($c^2_3 = 2.24$, P = 0.524). Also a model with equal transmission probabilities differs (with borderline significance) from the mixed model ($c^2_2 = 5.99$, P = 0.050). Unfortunately, several models involving an additive major gene could not be tested since the Mendelian mixed model, with d = 0.5, did not reach convergence. Therefore, the Mendelian recessive mixed model, with a small multifactorial component (H = 0.29) with a gene frequency of approximately 0.4, is the best model as indicated by the (**AIC**).

Table III - Segregation analysis of *Leishmania chagasi* infection.

Model	d	t	q	H	tAA	tAa	taa	*-2lnL*	*AIC*	*P*
1. Mendelian mixed	0.0*	2.386	0.373	0.284	[1]	[1/2]	[0]	318.44	326.44	
2. Mendelian mixed (d = 0)	[0]	2.388	0.372	0.285	[1]	[1/2]	[0]	318.50	324.50	0.81
3. No major gene	[0]	[0]	[0]	0.592	-	-	-	324.67	326.67	0.046

4. Sporadic	[0]	[0]	[0]	[0]	-	-	-	356.45	356.45	< 0.001
5. No multifactorial	0.238	2.340	0.393	[0]	[1]	[1/2]	[0]	320.58	326.58	0.144
6. Recessive Mendelian	[0]	1.841	0.439	[0]	[1]	[1/2]	[0]	322.84	326.84	0.13
7. Additive Mendelian	[0.5]	2.248	0.497	[0]	[1]	[1/2]	[0]	322.17	326.17	0.21
8. Dominant Mendelian	[1]	1.390	0.142	[0]	[1]	[1/2]	[0]	327.81	331.81	< 0.001

[ ] Parameter was fixed. * Parameter reached its bound

The probabilities of being affected for the three genotypes following the nine age-liability classes were determined according to the most parsimonious models, for recessive and additive inheritance (Table IV, based on model 6 of Table III and in Table V, based on model 7 of Table III).

Table IV - Probability of *Leishmania chagasi* infection based on a model where the susceptibility phenotype is due to a recessive gene*.

Age group (years)	Genotype	
	aa	AA or Aa
0-50	0.73995	0.02090
6-10	0.83381	0.04369
11-15	0.89228	0.07494
16-20	0.92797	0.11163
21-25	0.95040	0.15149
26-30	0.96506	0.19322
31-35	0.97499	0.23606
36-40	0.98191	0.27963

> 40	0.98875	0.34577

* Data are based on model 6 in Table III

Table V - Probability of *Leishmania chagasi* infection based on a model where the susceptibility phenotype is due to an additive gene*.

Age group (years)	Genotype		
	aa	Aa	AA
0-50	0.55695	0.04374	0.00018
6-10	0.64928	0.07096	0.00045
11-15	0.72634	0.10560	0.00096
16-20	0.78907	0.14713	0.00186
21-25	0.83917	0.19462	0.00333
26-30	0.87860	0.24698	0.00561
31-35	0.90931	0.30310	0.00895
36-40	0.93304	0.36197	0.01372
> 40	0.95860	0.45330	0.02446

* Data are based on model 7, in Table III

DISCUSSION

Cabello *et al.* (1995) observed familial aggregation of *Leishmania* infection in the same population of Jacobina. They investigated intrafamilial patterns of infection and found significant associations concerning father x offspring, mother x offspring, and sib x sib, in contrast with a nonsignificant parental association. The present study shows evidence of a major gene for human resistance/susceptibility *to L. chagasi* infection, with a gene frequency (**q**) around 0.4. The conditions of transmission probabilities to infer the presence of a major gene were satisfied.

In mice, the innate susceptibility to *L. donovani* has been shown to be controlled by a single autosomal gene located on chromosome 1 (Bradley, 1977; Bradley *et al.*, 1979). Additionally, other experimental infections have demonstrated that gene(s) from the same chromosome segment regulates resistance/susceptibility to several microorganisms such as: *S. typhimurium* (Plant and Glynn, 1974, 1996), *M. bovis* (Gros *et al.*, 1981;

Skamene *et al.*, 1982), *M. lepraemurium* (Brown *et al.*, 1982; Skamene *et al.*, 1984) and *M. intracellulare* (Goto *et al.*, 1984).

The presence of a major gene was also suggested to exist for a similar parasite (*L. peruviana*) (Shaw *et al.*, 1995). However, the genetic mechanism, presently suggested, should be taken as tentative, since problems of penetrance and dominance may confound the whole picture. The conclusions should be confirmed in other populations, as well as explored through both genetic linkage and genetic mapping starting on chromosome 2, which has a region homologous to the mouse chromosome 1. Since recent research reported that related traits (leprosy *per se*) may segregate linked to 2q markers, as a homologous *Lsh* gene should do (Abel *et al.*, 1998; Sachdeva *et al.*, 1996), studies on less environmentally influenced phenotypes, i.e., independent of a previous infection and less dependent on the prevailing environment conditions like the Mitsuda reaction, for instance (Feitosa *et al.*, 1996), must have precedence, due to the existence of apparently conflicting linkage studies (Shaw *et al.*, 1993; Levee *et al.*, 1994; Newport *et al.*, 1995). Other candidate gene regions have been suggested for human susceptibility in addition to NRAMP1 (cf. Blackwell, 1998) and must be investigated.

ACKNOWLEDGMENTS

RESUMO

Uma amostra de 502 indivíduos, pertencentes a 94 famílias de Jacobina (Estado da Bahia, Brasil), foi estudada com a finalidade de averiguar os mecanismos causais implicados na infecção por *Leishmania chagasi* (o agente causal do calazar, no hemisfério americano), medida pela reação intradérmica ao antígeno derivado desse parasita, utilizando análises de segregação complexa. Os resultados evidenciaram um mecanismo genético principal atuando sobre a infecção, com o gene recessivo responsável pela susceptibilidade tendo uma freqüência de aproximadamente 0,54. A hipótese da existência de um pequeno componente multifatorial (**H** = 0,29), agindo em conjunto com o gene principal recessivo (**q** = 0,37), não pode ser descartada.

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