Familial Analysis of Seropositivity to *Trypanosoma cruzi* and of Clinical Forms of Chagas Disease

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Abstract. A cross-sectional study was carried out in Água Comprida, MG, Brazil, a region previously endemic to Chagas disease whose vectorial transmission was interrupted around 20 year ago. A total of 998 individuals were examined for anti-*Trypanosoma cruzi* antibodies. Seropositivity was observed in 255 subjects (25.5%), and 743 subjects were negative. Forty-one families with 5–80 individuals with similar environmental conditions were selected for familial analysis. In 15 families, seropositivity to *T. cruzi* was observed in > 50% of individuals. The segregation analysis confirmed family aggregation for the seropositivity to the *T. cruzi*. Heart commitment was the major clinical form observed, and in six families, > 50% of the individuals display cardiopathy that may be attributed to *T. cruzi* infection. Our results support the hypothesis that there is a family aggregation for the seropositivity but without the effect of one major gene.

INTRODUCTION

Genetic studies on susceptibility to infectious diseases and their pathological consequences in human populations are relatively recent.[1–3] Several methods can be used to identify the genes that influence the host's susceptibility to pathogenic agents. Epidemiological studies suggest a familial aggregation with features associated with resistance or susceptibility that, with modern techniques of analysis, made clear the presence of genetic control by the main gene.[4]

Recent advances in statistics and molecular genetics allowed for in-depth investigation of both genetic and environmental factors that influence susceptibility to several infectious diseases.[2,5,6]

In the worldwide context, parasitic diseases represent an enormous onus, and nowadays, many studies are being carried out for the identification of genetic factors that may imply susceptibility for a variety of diseases.

Chagas disease, caused by the hemoflagellate protozoan *Trypanosoma cruzi*, is prevalent in Latin American populations with about 9–13 million individuals chronically infected. Forty million people still live in areas where risks of infection transmission exist.[7–9] Research carried out with experimental models and humans has shown a variation in the susceptibility to infection by *T. cruzi*, and possibly, genetic factors may play an important role in the susceptibility to the infection and in the development of lesions in the chronic phase.[10–17]

This study aims to verify the current prevalence of seropositivity, clinical forms, and familial aggregation of these characteristics in a population living in an endemic area where the vectorial transmission was interrupted.

MATERIALS AND METHODS

Study area. The study was performed in the Municipality of Água Comprida, (20°03′23″ S, 48°06′31″ W at 540 m above sea level), situated in the Vale do Rio Grande, South of Triângulo Mineiro, Minas Gerais State, Brazil. The city was an endemic area for Chagas disease and was included in the first National Campaign against *T. cruzi* that began in 1975. Epidemiological and entomological data showed evidence of the interruption of the vectorial transmission of the parasite to humans in 1999, and an international commission certified Brazil as free of transmission in 2005.[18,19]

Studied population. All individuals > 25 year old living in the rural and urban zones of the municipality were invited to participate in this study.

For the familial analysis the families were recorded as well as relationship, name, date of birth, gender, and time of exposure to the domiciliary triatomines of all the individuals to ensure correct identification. This information was double checked with another member of the family to avoid inconsistencies.

Ethical considerations. The protocol of this study was approved by the Ethical Committee on Research of the Federal University of the Triângulo Mineiro and local health authorities. Informed consent was obtained from all who were involved in the study.

Serological test. The detection of anti-*T. cruzi* antibodies was performed through passive haemaglutination techniques (Salck Laboratory, São Paulo, Brazil), enzyme-linked immunosorbent assay (ABBOTT, Brazil), and indirect immunofluorescence using FITC (Fluorescein isothiocyanate) conjugated to rabbit anti-human IgG (Sigma). Assays were done in accordance with orientations of each manufacturer, and the results were qualitatively expressed.

The individual who presented at least two positive reactions was considered positive.

Characterization of clinical forms. Clinical examination, radiography of the thorax contrasted with that of the esophagus and colon, and conventional 12-branch electrocardiogram were performed in all individuals. The individual was considered an indeterminate form carrier when presenting only positive serological reaction along with an absence of signs and symptoms and normal conventional electrocardiogram and radiography of the thorax, esophagus, and colon.[20] Cardiopathy was characterized by at least one of the following electrocardiographic alterations: atrioventricular blocks, intraventricular blocks (right bundle branch block and block of the anterosuperior division of the left branch), sinus bradycardia (with pre-mature ventricular contractions or primary and diffuse alterations of ventricular repolarisation), and pre-mature ventricular contractions (five or more per minute).[21] We considered the individual who

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presented with alteration of the esophagus and/or colon on barium-contrast radiological examination as digestive clinical form.[22,23] When both cardiac and digestive alterations existed, the clinical form was considered mixed.[21]

The characterization of clinical forms was realized in 224 subjects from the 41 families selected.

Statistical analysis. The Mann-Whitney non-parametric test for comparing clinical form, age, and gender of all the individuals was used. The χ^2 test was also used for comparing gender, serology, age, and clinical form of the positive individuals; $P < 0.05$ was considered significant.

Segregation analysis. Segregation analysis was performed using the computer program REGRESS in a model developed by Bonney.[24] All tests were performed using a type I error of 0.05. The major gene is not the only gene involved in the expression of the phenotype. A binary clinical phenotype (affected/unaffected by disease) specifies a regression relationship between each individual phenotype and explanatory variables. The dependence on phenotypes of preceding relatives is parameterized in terms of familial correlations: in the present study, father-offspring (FO) and sibling-sibling (SS) correlations. The effect of a major gene is defined by q (the frequency of allele A that is assumed to pre-dispose to infection), αAA, αAa, and αaa (the genotypic means of individuals with genotypes AA, Aa, and aa, respectively); the regression coefficient is associated with the time of exposure.

RESULTS

The study encompassed 998 individuals distributed in 114 families. Of these, 468 (46.9%) were male, and the mean age was 41.6 year (SD ± 42.4 year). The mean age was 38.5 year (SD ± 20.2 year) for females. No significant difference was observed on mean age and gender ($P = 0.1344$). The research for anti-*T. cruzi* antibodies in these individuals showed that 255 (25.6%) were serologically positive, 114 of which were males (44.7%); 743 (74.5%) individuals presented with negative serology, 354 of which were males (47.6%). No significant difference was observed with seropositivity and gender. Forty-one families with at least five individuals were selected for familiar analysis, which totaled 526 individuals: 224 (42.6%) with positive serology results, 235 (44.7%) with negative serology results, and 67 (12.7%) without serology results. In analyzing the familial serological positivity, it was observed that, in 15 families, > 50% of the individuals presented positive serology for anti-*T. cruzi* antibodies (Table 1), which showed aggregation in some families. Among the 224 seropositive individuals of the selected families, 151 were submitted to clinical and laboratorial examination and than grouped
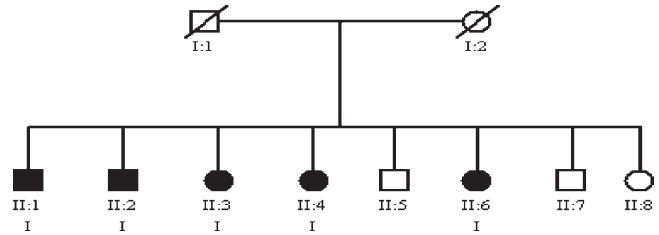

FIGURE 1.   Pedigree showing a family with 100% of the individuals with the indeterminate form of Chagas disease. (Circles, females; squares, males; filled symbols, individuals with positive serology to Chagas disease; symbols with trace, dead individuals; I, indeterminate form.)

on clinical forms of chronic Chagas disease: 58 (38.4%) presented the indeterminate form, 72 (47.7%) presented the cardiac form, 10 (6.6%) presented the digestive form, and 11 (7.3%) presented the mixed form. The subjects with cardiac clinical form were older than those individuals with indeterminate clinical form (62.7 year [SD ± 11.7 year] and 54.9 year [SD ± 13.2 year], respectively; $P = 0.002$). It was not possible to examine for diagnosis of clinical form in 73 individuals. Of the 41 families analyzed, 12 did not present any individual with the cardiac form (Figure 1). However, in six families, the cardiac form was observed in > 50% of individuals (Table 2; Figure 2), and in two families, 100% of the individuals presented the indeterminate form.

The evidence of a possible family aggregation in relation to the seropositivity was confirmed by segregation analysis. The results in Table 3 show strong evidence for familial aggregation of serological positivity to *T. cruzi* ($\chi^2 = 22.8$; gl = 4; $P < 0.001$), because the sporadic model without familial correlation was rejected. Concerning clinical forms, there was a tendency for aggregation in certain families in cardiac and indeterminate forms. The small number of cases of digestive and mixed forms did not show the evidence of a possible familial aggregation.

DISCUSSION

In this study, the research for anti-*T. cruzi* antibodies was performed in individuals > 25 year old, and 25.56% were found to have positive serology. Despite the high positivity, a decrease over the years as a consequence of the interruption of vectorial transmission was verified. In Brazil, the prevalence of *T. cruzi* has reduced in incidence by 98% from 1980 to 1999.[25]

In the distribution of clinical forms in the 151 individuals analyzed, 47.7% presented the cardiac form, 38.4% presented the indeterminate form, 6.6% presented the digestive form,

TABLE 1

Distribution of the families according to the percentage of individuals serologically positive for Chagas disease in Agua Comprida City, Minas Gerais State, Brazil

Positivity	Number of families	Percentage
1–25%	5	11.1
26–50%	21	46.7
51–75%	11	24.4
≥ 76%	4	8.9
Total	41	100.0

TABLE 2

Distribution of the families according to the percentage of individuals with chagasic cardiopathy in Agua Comprida City, Minas Gerais State, Brazil

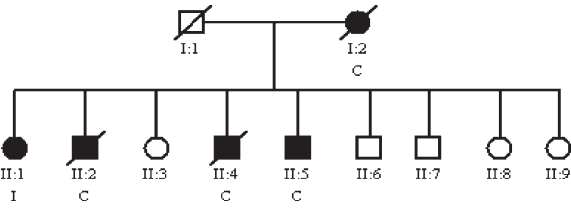| Cardiac form	Number of families	Number of individuals	Percentage of total families
Absent	12	40	29.3
1–25%	6	41	14.6
26–50%	17	116	41.5
51–75%	2	11	4.9
≥ 75%	4	16	9.7
Total	41	224	100.0

FIGURE 2. Pedigree showing a family with > 50% of the individuals with the cardiac form of Chagas disease. (Circles, females; squares, males; filled symbols, individuals with positive serology to Chagas disease; symbols with trace, dead individuals; I, indeterminate form.)

and 7.3% presented the mixed form. These data are similar to those found by Pereira and Coura[26] in Virgem da Lapa, Minas Gerais. The manifestation of clinical forms has regional characteristics, and the State of Minas Gerais is one of those that presents a predominance of cardiac form. Chapadeiro and others[27] showed 41.8% cardiac impairment among the individuals seropositive to Chagas disease found in the region of Triângulo Mineiro. Other authors pointed out that the percentage of individuals with chagasic cardiopathy in endemic areas varied from 8% to 50%.[28–34]

The frequency of the digestive form of this casuistry (6.3%) is included in that signalized in other endemic areas of Brazil, and it oscillates between 3% and 10% of the population living in these areas.[26,35]

The differences in clinical form presentations have raised questions about the potential for evolving forms. Patients are able to remain in an indeterminate form, or they can progress to the cardiac, digestive (megas), or mixed forms.[36] In endemic areas where there still is a vector transmission for Chagas disease, it is important to highlight the role of re-exposition. In the case of the endemic area of Água Comprida, vectorial transmission of Chagas disease has been interrupted since 1985 and continues that way through the present.[37,38]

At the present, there are no solid explanations that justify this difference of behavior, although some hypotheses try to associate it to different factors connected to the infective sampling of T. cruzi, the socioeconomic status of the patient, or the immune response in the interaction with this parasite.[39]

The clinical diagnosis of the 73 individuals was not possible, because since 1980, several clinical, epidemic, immunological, and therapeutic studies were performed in this area. For this reason, those patients, in the moment of the investigation, did not agree to participate in the evaluation.

The influence of the genetic characteristics of the host on susceptibility to other human parasitic infections was not easy

proven, probably because environmental factors, such as vectors and reservoirs, can play an important role. It is also thought that alteration in parasite characteristics contributes to the heterogeneity of the manifestations observed in individuals in endemic areas.[40] The idea of susceptibility genes of the host has developed recently. However, solid evidence points out that the intrinsic capacity for human resistance to parasitic infections varies widely among individuals and may be determined by genetic polymorphism of the host.[41] A few genetic studies on the susceptibility to infectious diseases in human populations have come to light, and recent advancement in genetics has allowed for better exploration of these factors in a large number of infectious diseases. Much controversy exists about the factors that could influence the evolvement of Chagas disease, because some patients develop severe forms, whereas other ones remain asymptomatic for their whole lives.

In this study performed in 41 families, it was possible to observe the familial aggregation of serological positivity to T. cruzi. Similar data regarding the familial aggregation of seropositivity to T. cruzi were found by Williams-Blangero and others[15] in a region of Goiás State, Brazil. However, the mean number of individuals per studied family does not allow comparison between the studies. The familial aggregation of seropositivity to T. cruzi is normally ascribed to the bigger or smaller presence of triatomines in the homes as well as to habitation conditions. In this study, distinct familial seropositivity was observed in families homogeneously exposed to domiciliary vectors. However no evidence of a major gene control was observed, it does not exclude the participation of genetic factors. Moreover, these results may indicate a multigenetic and complex host–parasite relationship that can affect the susceptibility to infection and the potential for the development of clinical forms of Chagas disease.

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TABLE 3
Segregation analysis in 41 families with individual serological positivity

Model and hypothesis	Q*	α_{aa}†	α_{Aa}	α_{AA}	γ_{PO1}‡	γ_{SS1}	γ_{PO2}	γ_{SS2}	β_{dur}§	τ_{AAA}¶	τ_{AAa}	τ_{Aaa}	−2l nL + C**
I. Sporadic	[0]	−6.22	[=α_{aa}]	[=α_{aa}]	[0]	[0]	[0]	[0]	1.77	–	–	–	23.1
II. Familial dependence													
a. Father-offspring and sib-sib	[0]	−4.49	[=α_{aa}]	[=α_{aa}]	−0.95	−0.34	−0.03	0.19	1.34	–	–	–	0.3
III. Mendelian major gene													
a. Codominant with residual familiar dependence	0.62	−6.78	−11.0	−11.0	−1.55	0.0	−0.49	0.0	2.79	1	0.5	0.0	0.0

χ^2 = 22.8; gl = 4; $P < 0.001$.
* Frequency of allele A pre-disposing to T. cruzi infection.
† Baseline risks of being T. cruzi positive on logit scale corresponding to three genotypes: AA (α_{AA}), Aa (α_{Aa}), and aa (α_{aa}).
‡ Regression coefficients associated with the following familial dependences: father-offspring (γ_{PO1}, γ_{PO2}) and sib-sib (γ_{SS1}, γ_{SS2}).
§ Regression coefficient associated with the time of exposure to the domiciliary triatomines (β_{dur}).
¶ Probabilities of transmitting A for individuals AA (τ_{AAA}), Aa (τ_{Aaa}), and aa (τ_{Aaa}).
** C represents twice the log likelihood (2l nL) of the general model.

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