

Authors Reply

Adaptive and genetic evolution of *Toxoplasma gondii*: a host-parasite interaction

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Dear Editor:

This letter is a response to the excellent and very productive suggestions and comments by Dr. Oliveira in the *Letter to the Editor* titled "**Polymorphisms in *Toxoplasma gondii*: role of atypical strains in unusual clinical manifestations of toxoplasmosis**". The observations documented by the author concerning the clinical manifestations in humans, has been reported not just in Rio Grande do Norte, but also in newborns¹ and AIDS patients^{2,3} from Minas Gerais and Sao Paulo, and many other places in South America, indicating a high genetic diversity that includes atypical genotypes. In veterinary medicine, many different genotypic profiles have also been reported in a wide range of domestic and wild intermediate hosts, some of which are considered sources of infection for humans, and others, just sentinels^{1,4-6}.

Several factors can influence the occurrence of the disease. These include dose, parasite stage, initiating infection, parasite genotype, host genotype, and various factors that affect the host's immune status, especially interaction of, and concomitant infection with other pathogens⁷. In eukaryotic parasites like *Toxoplasma gondii*, virulent alleles at multiple locations in the genome determine the pathogenicity⁸. Overall, the geographic origin of the patients influence the presence of different *T. gondii* strains; however, virulent strains containing type I, or atypical alleles are known to be more pathogenic or more likely to cause severe diseases in patients. The parasite's adaptation to different geographic regions and hosts may contribute to the occurrence of polymorphism. As reported previously, Central America and South America present a wide genetic diversity of *T. gondii* strains as compared to that in Europe and North America⁴, and may reflect an ancient South American origin for the species⁹. Therefore, there is a high probability that after completion of every new study conducted in South and Central

America, a new atypical genotypic profile will be identified⁵. The original genetic diversity of *T. gondii* strains predominant in North America and Europe may have been very wide, although a recent increase in distribution of the domestic cat (an Old World species), since the sixteenth century, may have favored a specific subset of pre-adapted genotypes¹⁰. In addition, virulence profiles indicate more virulent strains in Central American and South American isolates, corroborating to a more diverse genotypic profile.

According to Müller and Howard¹⁰, the evolution of *T. gondii* is directly related to its relationship with the domestic cat, as a definitive host; however, the absolute dominance of the domestic cat is only recent, and it is unknown whether any genomic co-adaptation has already occurred. It is known that many atypical genotypes differ in pathogenicity and transmissibility from typical genotypes¹¹, which allow us to propose a possible link between the infection in humans and genotypic profile of *T. gondii* strain.

The atypical strains result from selective pressure over the oldest ancestry, with a substantial influence on virulence. Recombination can occur even without the presence of the definitive hosts, when the intermediate host, that is, human, ingests the evolutive forms from other intermediate hosts (sheep, pork, chicken)². In this way, the frequent ingestion of raw or undercooked meat, and oocysts on the ground by birds, expose humans, mammals, and birds to infections and contribute to a high degree of polymorphisms and variety of atypical isolates. The parasite's dissemination may occur primarily by clonal reproduction, through sexual recombination among different strains by assexuate replication¹².

Clonality is evidenced by the isolation of strains with identical genotypes, from different hosts of different geographic areas.

In the same way, the strongest evidence for a definite recent causal relationship between specific features of the pathogen and the host's genome is reciprocal polymorphism, with an experimentally demonstrable causal chain. An important clue for atypical strains causing unusual clinical manifestations is that the infection also modifies the host's genome. The mammalian genome has clearly been influenced by infection. The

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Received 12 June 2017
Accepted 27 June 2017

extraordinary genomic complexity of the re-arranging receptors of lymphocytes, and the complex array of immune functions assembled in the mammalian major histocompatibility complex are indications of millions of years of pathogen pressure¹⁰.

The pattern of host-pathogen co-evolution depends on the extent to which the host's resistance reduces pathogen transmission. Wild and domestic felids, the definitive hosts for *T. gondii*, present an important role to the evolution of the parasite. *T. gondii* can evolve once it completes its life cycle in a new definitive host. This was observed from studies conducted with mice, which demonstrated that the intermediate host develops neophobic behavior and avoids new stimuli. Therefore, in response to the parasite's manipulation caused by the invasion of lesions sites, or biochemical signals, infected hosts show more active behavior, and reduced neophobic behavior, making the parasite more prone to completing its life cycle. *T. gondii* is able to determine a delicate balance between parasitism and the host's immune response, which is supported by the mode of infection, strain, immune and cytokine response, as well the interaction of host genes and parasite genes^{10,11}, characterizing a behavioral manipulation, and conferring a selective advantage to *T. gondii*. In other words, *T. gondii* is an opportunistic parasite for humans and other animals (i.e., cats and dogs), as published before.

Humans, while abundantly and globally infected by *T. gondii* at a rate of over 1% per year of age, are inaccessible as prey for domestic cats¹⁰, as are other mammals or bird species. The parasite needs to control the progress of the infection. It is not important to kill the host. At the same time, the parasite cannot be defeated by the human immunity. The parasite is completely uninterested in defeating, or being defeated by human immunity. However, in the presence of such an event, immunity is normally sufficient to reduce morbidity from *T. gondii* infection to very low levels. The parasite's exceptional ability to use the host's immunity in general, as a trigger for bradyzoite conversion, means that infected humans do carry cysts and thus, sufficient immunity for parasite elimination is yet to be recorded in man. If, however, the host and the pathogen show reciprocal polymorphism in virulence and resistance, it would suggest that the system is under selection. The parasitic strategy of *T. gondii* involves securing a permanent residence in the host, and awaiting transmission. The adaptive immune system shows little co-adaptation to different pathogens, at the genomic level; it is an anti-pathogenic machine. In this way, the allelic frequencies will depend on the ratio of the intensity of selection pressures of the parasites¹⁰.

In this way, upcoming human and animals should focus on the correlation between the genome (mainly atypical isolates) and corresponding unusual clinical manifestations, emphasizing on longitudinal studies. This will enable understanding of the interaction between host genomes (definitive and intermediate hosts) and environmental variables, with potential polymorphisms being introduced into the parasite population, thereby, changing the clinical patterns of the disease. Evolutionary studies are essential to analyze host-parasite interactions, evasive

mechanisms of the host's immune response attack developed by the definitive and intermediate hosts, as well as the host's and parasite's gene polymorphism presented by time according to environmental and genetic adaptation. This promotes phenotypic changes like those observed in the unusual clinical symptomatology, observed in human toxoplasmosis caused by atypical strains.

Conflict of interest

The authors declare that there is no conflict of interest.

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