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Host genetics and parasitic infections

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Abstract

Parasites still impose a high death and disability burden on human populations, and are therefore likely to act as selective factors for genetic adaptations. Genetic epidemiological investigation of parasitic diseases is aimed at disentangling the mechanisms underlying immunity and pathogenesis by looking for associations or linkages between loci and susceptibility phenotypes. Until recently, most studies used a candidate gene approach and were relatively underpowered, with few attempts at replicating findings in different populations. However, in the last 5 years, genome-wide and/or multicentre studies have been conducted for severe malaria, visceral leishmaniasis, and cardiac Chagas disease, providing some novel important insights. Furthermore, studies of helminth infections have repeatedly shown the involvement of common loci in regulating susceptibility to distinct diseases such as schistosomiasis, ascariasis, trichuriasis, and onchocerciasis. As more studies are conducted, evidence is increasing that at least some of the identified susceptibility loci are shared not only among parasitic diseases but also with immunological disorders such as allergy or autoimmune disease, suggesting that parasites may have played a role in driving the evolution of the immune system.

Keywords: Genetic epidemiology, genome-wide association studies, leishmaniasis, lymphatic filariasis, malaria, onchocerciasis, schistosomiasis, soil-transmitted helminth diseases, trypanosomiasis

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The MalariaGEN Consortium**.** Reappraisal of known malaria resistance loci in a large multicentre study. Under revision by Nature Genetics[1].

Introduction

Parasitic diseases represent a very important public health problem, mainly in the tropical and subtropical regions of the world (Table 1). The heaviest death toll is imposed by malaria, with approximately 600 thousand reported fatalities every year. However, parasites can cause not only acute and lethal illnesses but also chronic diseases with diverse impacts ranging from compromised organic functions to malnutrition, impaired growth and learning abilities, and increased susceptibility to other infections.

It is therefore likely that all major parasites play a role as selective factors in shaping the evolution of the human genome, promoting a rise in the frequency of protective alleles (e.g. for malaria [2]). Actually, for many parasitic diseases, a heritable component has been demonstrated. Evidence has been gained with a variety of approaches, including twin studies, observation of familial clustering, pedigree-based variance component analysis and segregation analysis, and studies of ethnic groups that share the same environmental exposure but show different susceptibilities [2–10]. Although parasitic diseases are clearly of multifactorial origin, the genetic architecture underlying susceptibility varies, with two possible extremes being represented by malaria, in which the genetic component is more probably explained by the additive effect of many loci with small to modest penetrance [11], and *Schistosoma* infection, in which one major locus with high penetrance seems to be involved [12].

TABLE 1. Major human parasitic diseases

Disease	Phylum	Species	Transmission	Distribution	Infections [a]	Deaths [b]	DALYs [b]
Malaria	Apicomplexa	*Plasmodium falciparum*, *P. malariae*, *P. vivax*, *P. ovale*, *P. knowlesi*	Bite of female mosquitoes (*Anopheles*)	Tropical and subtropical areas	~258 million [c]	589 218	55 413 529
Schistosomiasis	Platyhelminthes	*Schistosoma mansoni*, *S. haematobium*, *S. japonicum*, *S. mekonji*, *S. intercalatum*	Contaminated fresh water [d]	Tropical and subtropical areas	~243 million	23 313	3 971 096
Leishmaniasis	Sarcomastigophora	*Leishmania* species	Bite of female sand flies (*Phlebotomus*, *Lutzomya*)	Tropical and subtropical areas	0.8–1.6 million [c]	53 675	3 754 202
Hookworm disease	Nematoda	*Ancylostoma duodenalis*, *Necator americanus*	Contaminated soil	Worldwide [e]	~740 million	3	3 158 856
Lymphatic filariasis	Nematoda	*Wuchereria bancrofti*, *Brugia malayi*, *B. timor*	Bite of female mosquitoes (*Aedes*, *Anopheles*, *Culex*, *Mansonia*)	Tropical areas	~120 million	5	2 740 426
African trypanosomiasis (sleeping sickness)	Sarcomastigophora	*Trypanosoma brucei gambiense*, *T. b. rhodesiense*	Bite of tsetse fly (*Glossina*)	Sub-Saharan Africa	~20 000 [c]	19 026	1 345 594
Ascariasis	Nematoda	*Ascaris lumbricoides*	Contaminated soil	Worldwide [c]	≈1.2 billions	2991	1 253 785
Trichuriasis	Nematoda	*Trichuris trichura* (whipworm)	Contaminated soil	Worldwide [f]	~795 million	0	629 901
Onchocerciasis (river blindness)	Nematoda	*Onchocerca volvulus*	Bite of blackfly (*Simulium*)	Africa, foci in Latin America and the Middle East	~26 million	1	564 059
American trypanosomiasis (Chagas disease)	Sarcomastigophora	*Trypanosoma cruzii*	Bite of triatomine bugs (*Rhodnius*, *Panstrongylus*, *Triatoma*)	Latin America	7–8 million	7356	499 067

DALY, disability-adjusted life-year.
[a]Data on infection cases are based on the most recent WHO reports on individual parasites (prevalent cases if not specified otherwise).
[b]Data on deaths and DALYs are based on the WHO Global Health Observatory Data Repository for 2011.
[c]Incident cases.
[d]*Biomphalaria*, *Bulinus*, *Neotricola* and *Oncomelania* snails are intermediate hosts.
[e]Highest prevalence in warm and moist climate areas, and areas with poor sanitation.
[f]Highest prevalence in tropical and subtropical areas, and areas with poor sanitation.

Genetic epidemiology studies are aimed at identifying the genetic factors responsible for heritability through association or linkage with the phenotype of interest [13]. The identification of susceptibility loci can provide important insights into the mechanisms of protective immunity and pathogenesis, and genetic epidemiology studies can be therefore regarded as observational studies of immunology *in natura*, complementary to *in vitro* and *in vivo* experimental studies [14].

In recent years, major advances have been achieved in the study of protozoa by the creation of consortia, namely MalariaGEN [15] and LeishGEN [16], that have allowed the collection of unprecedently large and multicentre samples, and the standardization of case definitions and laboratory procedures. Furthermore, genome-wide association studies (GWASs) of severe *Plasmodium falciparum* malaria [17–19], visceral leishmaniasis (VL) [16] and Chagas disease [20] have been conducted.

Regarding helminths, increasing evidence has emerged that a common genetic basis exists for susceptibility to different species, as will be discussed. Although no GWAS has been conducted to date, an interesting new approach has been proposed to identify candidate genes at the genome-wide level, by searching for polymorphisms that show strong correlations with the diversity of the prevalent helminth species in distinct geographical areas [21]. The same approach has been successful in identifying known loci involved in resistance to protozoan infections [22].

An update per parasite in the field follows. Genetic epidemiology studies of susceptibility to parasitic diseases were searched for in the existing literature with the following terms and Boolean operators: '(genetic OR polymorphi*) AND (association OR link* OR genome scan OR genome wide) AND (parasitic disease OR parasite)' [23]. Only articles written in English for which abstracts were available and that described studies based on human subjects were included in the search. The search was frozen on 8 April 2014. Previous reviews on the subject were also looked for, and particular emphasis has been given in the following paragraphs to more recent studies.

Malaria

Malaria is caused by apicomplexan parasites of the genus *Plasmodium*, which are transmitted by *Anopheles* blood-sucking