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Feature Review

Neglected Tropical Diseases in the Post-Genomic Era

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Neglected tropical diseases (NTDs) are a group of viral, bacterial, and eukaryotic parasitic diseases that are especially endemic in low-income populations, with a large health and economic impact on both the developing and developed world. The structure and dynamics of the genomes of the organisms causing these diseases, as well as the modes of expression, exchange, and transmission of their genetic information, often deviate from those found in classical, model organism-centric textbooks. We assess the role of basic and applied genetic research in our understanding of key aspects of their biology and evolution, and discuss the impact of novel high-throughput approaches spawned by the post-genomic era on the development of next-generation drugs, vaccines, molecular epidemiology, and/or diagnostic tools for these important pathogens.

Trends

Neglected tropical diseases have a large health and economic impact on human populations.

The addition of significant effort and resources can move an organism off of the NTD list.

The organisms causing these diseases often have unique genetic features.

We describe the role that genetic research had in our understanding of their biology and evolution.

We discuss the impact of novel high-throughput approaches spawned by the post-genomic era.

Neglected Tropical Diseases and Their Pathogens

NTDs are a heterogeneous group of infectious diseases unified not by pathophysiology, evolution or geography – they can be found outside the tropics – but by their endemicity, especially in low-income populations in developing regions of Africa, Asia, and the Americas, thus perpetuating the poverty of the poorest people in the world [1,2]. In addition to being major pressing public health issues, most NTDs are zoonotic, thus posing an additional economic burden by affecting reliance on livestock for sustainable human development [1,2]. Importantly, the 17 illnesses currently classified as NTDs by the 2012 London Declaration (compiled in Table 1) are preventable and most are treatable. However, they still threaten the lives of more than 1 billion people worldwide [3]. Moreover, NTD outbreaks associated with previously unrecognized biological or epidemiological features were recently reported [4,5].

The causative agents of NTDs (henceforth NTD pathogens) represent a wide phylogenetic sampling of parasitic organisms, which include viruses, bacteria and eukaryotes (both unicellular protozoa and metazoan worms) (Table 1). They often display intricate life cycles, involving multiple developmental forms, both free-living and/or parasitic for either insect vectors or intermediate hosts. NTD pathogens use different strategies to ensure entry, infectivity, survival, and transmission to and from the human host, in which they trigger a wide spectrum of disease-associated pathologies. In accordance with this great biological diversity, the structure and dynamics of their genomes are fairly disparate. At the core of this phenomenon, a myriad of genetic transmission strategies have been unveiled, ranging from true haploid bacteria with a striking capacity for recombination and/or horizontal gene transfer (HGT), to asexual or rarely sexual protozoa, to classical, obligate sexual metazoan helminths (see below). These genetic exchange and/or reproductive strategies, in turn, play a key role in shaping the population structures of NTD pathogens and thus have major implications for the development, evaluation, and application of diagnostic, chemotherapeutic, or vaccine-based control strategies.

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Table 1. The 17 Neglected Tropical Diseases[a]

Disease	Causative Agent	Taxonomy Notes	Genomic Data Available
Buruli ulcer	*Mycobacterium ulcerans*	Actinobacteria (Gram positive)	Complete genome available [144]. https://www.patricbrc.org/ [145].
Chagas disease	*Trypanosoma cruzi*	Kinetoplastid Protozoa	Draft genomes of TcI [146], TcII and TcVI (hybrid) [147] lineages available. Projects to sequence genomes from other lineages are underway. http://tritrypdb.org [148].
Dengue	Dengue virus	Flavivirus	Genomes for all dengue virus serotypes (DENV-1–4) are available (reviewed in [149]), and functional RNA elements of the genome have been described [150]. http://www.viprbrc.org/ [151].
Dracunculiasis (Guinea worm disease)	*Dracunculus medinensis*	Nematoda (roundworms)	Sequencing underway at WTSI.
Echinococcosis	*Echinococcus granulosus, E. multilocularis*	Platyhelminths (flatworms), Cestoda	Complete genomes available [17,152].
Foodborne trematodiases (clonorchiasis, ophisthorciasis, fasciolasis, paragonimiasis)	*Clonorchis* spp., *Opisthorchis* spp., *Fasciola* spp., and *Paragonimus* spp.	Platyhelminths (flatworms), Trematoda	Draft genome for *Fasciola hepatica* available [153].
Human African trypanosomiasis (sleeping sickness)	*Trypanosoma brucei*	Kinetoplastid Protozoa	Complete reference genome available [154]. Genomes from different subspecies and strains/isolates also available [49,155]. http://tritrypdb.org [148].
Leishmaniasis	Several species of *Leishmania*	Kinetoplastid Protozoa	Complete reference genome available [80]. Genomes from different subspecies and strains/isolates also available [82,156,157]. http://tritrypdb.org [148].
Leprosy	*Mycobacterium leprae*	Actinobacteria (Gram positive)	Complete genome sequence of extant and medioeval isolates [158,159]. https://www.patricbrc.org/ [145].
Lymphatic filariasis	*Wuchereria bancrofti, Brugia malayi*, and *Brugia timori*	Filarial worms (Filarioidea); Nematoda (roundworms)	Complete genome sequence of *Brugia malayi* (and its endosymbiont) available [160]. Pre-publication draft genome data for *Wuchereria* and other filarial worms are available at the FWD.
Onchocerciasis (river blindness)	*Onchocerca volvulus*	Filarial worms (Filarioidea); Nematoda (roundworms)	Draft, partially assembled shotgun sequences are available (GenBank CBVM000000000).
Rabies	Rabies virus	Lyssavirus	Complete reference genome available [161]. http://www.viprbrc.org/ [151].
Schistosomiasis	Several species of the `genus *Schistosoma*: *S. haematobium* (urogenital) and any of *S. guineensis*, *S. intercalatum*, *S. mansoni*, *S. japonicum*, and *S. mekongi* (intestinal)	Platyhelminths (flatworms), Trematoda	Three genome sequences are available (*S. mansoni*, *S. japonicum*, *S. haemotobium)*, together with high-quality transcriptome data [16,162,163]. http://schistodb.net [164].

Glossary

Aneuploidy: a condition in which the number of chromosomes in the nucleus of a cell is not an exact multiple of the haploid number of chromosomes for a particular species.

Biovars: variant prokaryotic 'type' that differs physiologically and/or biochemically from other 'types' in a particular species. In the case of *C. trachomatis*, biovars differ both in their antigenic properties and in their pathotype (i.e., in their pathogenicity in a specific host).

Genetic hybridization: interbreeding/sexual recombination between genetically distinct individuals to produce an individual with different alleles of the same gene. Hybridization as used here refers to the genetic offspring produced from interbreeding between individuals of different species or subspecies to produce a stable offspring that carries alleles from each parent.

Introgression: the transfer of genetic material from one species to another as a result of genetic hybridization followed by repeated backcrossing (sexual recombination) with the original 'parent' species as opposed to the donor of the transferred genetic material.

Kinetoplast DNA: the kinetoplast is a network of circular DNA (termed kDNA) inside a large mitochondrion that contains many copies of the mitochondrial genome. It is only found in protozoa of the order Kinetoplastida. The kinetoplast contains circular DNA in two forms, maxicircles and minicircles, which are concatenated to form a network. During cell division, replication of this network requires that these rings are disconnected from the parental kinetoplast and subsequently reconnected in the daughter kinetoplast.

Multi-locus sequence typing (MLST): a DNA amplification and sequencing technique used to characterize pathogen isolates. The technique is based on genotyping DNA fragments from 7–8 independent genomic loci, usually housekeeping genes.

Mosaic aneuploidy: a mixed population of cells having chromosomes displaying extra, or fewer, copies than normal (e.g., haploid, diploid, triploid).