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Viral pathogen discovery[☆]

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Viral pathogen discovery is of critical importance to clinical microbiology, infectious diseases, and public health. Genomic approaches for pathogen discovery, including consensus polymerase chain reaction (PCR), microarrays, and unbiased next-generation sequencing (NGS), have the capacity to comprehensively identify novel microbes present in clinical samples. Although numerous challenges remain to be addressed, including the bioinformatics analysis and interpretation of large datasets, these technologies have been successful in rapidly identifying emerging outbreak threats, screening vaccines and other biological products for microbial contamination, and discovering novel viruses associated with both acute and chronic illnesses. Downstream studies such as genome assembly, epidemiologic screening, and a culture system or animal model of infection are necessary to establish an association of a candidate pathogen with disease.

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Current Opinion in Microbiology 2013, 16:468–478

This review comes from a themed issue on **Host–microbe interactions: viruses**

Edited by **Carlos F Arias**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 29th May 2013

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<http://dx.doi.org/10.1016/j.mib.2013.05.001>

Introduction

The identification of novel pathogens has a tremendous impact on infectious diseases, microbiology, and human health. Nearly all of the outbreaks of clinical and public health importance over the past two decades have been caused by novel emerging viruses, including Severe Acute Respiratory Syndrome (SARS) coronavirus [1], Sin Nombre hantavirus [2], 2009 pandemic influenza H1N1 [3,4], and the recently described coronavirus EMC [5–7] and H7N9 avian influenza viruses [8], with

most originating from animal reservoirs. Changes in the environment, globalization, growth of wet (live animal) markets, and the rapid expansion of the human population into wildlife habitats all promote the rapid spread of previously unidentified pathogens that are capable of causing widespread and devastating epidemics of human illness [9]. Arthropods such as mosquitoes and ticks are vectors for emerging pathogens including West Nile virus [10,11], and the Severe Fever and Thrombocytopenia Syndrome (SFTS) [12,13] and Heartland bunyaviruses [14]. Moreover, the link between new viruses and disease is not only restricted to acute illnesses, but also can be seen in chronic disease states, as demonstrated by the strong association between infection by the novel Merkel cell polyomavirus (MCPyV) and a rare, highly aggressive skin tumor in elderly patients [15].

Currently available diagnostic tests for pathogens are generally narrow in scope and fail to detect an agent in a significant fraction of cases. Traditional methods such as culture, serology, or targeted nucleic acid-based testing, such as specific polymerase chain reaction (PCR), have limited utility in investigations where there is no *a priori* knowledge of the identity of potential infectious agents. Notably, in certain infectious diseases such as encephalitis, conventional testing fails to identify a pathogen in up to 70% of cases [16–18]. In contrast, state-of-the-art genomic technologies such as pan-microbial microarrays or unbiased next-generation sequencing (NGS) can be attractive tools for broad-based pathogen discovery. Nearly all infectious agents, with the sole exception of prions [19], contain either RNA or DNA, and are thus amenable to nucleic acid-based detection. In principle, these technologies are capable of comprehensively identifying all potential pathogens in clinical samples from humans and animals. This review will describe the genomic approaches for pathogen discovery currently being employed in the field, and highlight recent examples of their use in the discovery and characterization of novel viral pathogens (Table 1).

Genomic approaches for pathogen discovery

Pathogen discovery entails the use of genomic-based methods to identify novel microbes, followed by further investigation to determine potential associations with disease (Figure 1). As a pathogen discovery tool, consensus PCR uses degenerate primers to detect conserved sequences that are broadly shared between members of a group. This approach was recently used to identify novel paramyxoviruses in samples from large-scale surveys of bats and rodents [20–22] and emerging viruses such as coronavirus EMC, the cause of a new severe and

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Table 1

Some recent examples of viral pathogen discovery^d

Name ^a	Detection platform	NGS bioinformatics approach	Disease association	Strength of association ^c
Coronavirus-EMC	Culture and 454 NGS [7]	<i>De novo</i> genome assembly	Severe pneumonia (humans)	++
SFTS (severe fever with thrombocytopenia virus)	Illumina NGS [12]	Subtraction and BLAST search	Severe fever with thrombocytopenia	++
Heartland bunyavirus	Culture and 454 NGS [14]	BLAST search and <i>de novo</i> gene assembly	Severe febrile illness	++
MCPyV (Merkel cell polyomavirus)	454 NGS [15]	Subtraction and BLAST search	Merkel cell carcinoma (MCC)	++
Bat paramyxoviruses	Consensus PCR [20–22]	N/A	–	–
Raccoon polyomavirus	Consensus PCR and RCA [38]	N/A	Brain tumors (raccoons)	++
HPyV6 and HPyV7 (human polyomaviruses 6 and 7)	RCA [39]	N/A	N/A	–
TSPyV (trichodysplasia spinulosa-associated polyomavirus)	RCA [40]	N/A	Trichodysplasia spinulosa	++
2009 pandemic influenza A(H1N1) ^b	Microarray and Illumina NGS [51]	Subtraction and BLAST search	Febrile illness	++
	454 NGS [110,111]	BLAST search	Febrile illness	++
	Illumina NGS [112]	BLAST search	Febrile illness	++
TMAV (titi monkey adenovirus)	Microarray and Illumina NGS [52]	BLAST search	Pneumonia (titi monkeys)	++
BASV (Bas-Congo virus), a rhabdovirus	Illumina NGS [58]	Subtraction, BLAST search, and <i>de novo</i> genome assembly	Acute hemorrhagic fever	++
Novel circoviruses and cycloviruses in humans and monkeys	454 NGS [59]	Subtraction and BLAST search	Diarrhea	–
Human klassevirus/salivirus	Illumina NGS [61]	Subtraction and BLAST search	Diarrhea	–
	454 NGS [60,62]	Subtraction and BLAST search	Diarrhea	–
MWPyV/HPy10/MXPYV (MW polyomavirus)	454 NGS [63]	Subtraction and BLAST search	Diarrhea	–
	Illumina NGS [64]	Subtraction and BLAST search	Diarrhea	–
	Illumina NGS [65]	BLAST search	WHIM syndrome	–
HPyV9 (human polyomavirus 9)	Illumina NGS [66]	Subtraction and BLAST search	–	–
	Consensus PCR [24]	N/A	–	–
Human bufavirus	454 NGS [67]	Subtraction and BLAST search	Diarrhea	–
HAsTV-PS (human astrovirus Puget Sound)	454 NGS [68]	Subtraction and BLAST search	Encephalitis	++
Human enterovirus 109	Consensus PCR and Illumina NGS [69]	Subtraction and BLAST search	Acute respiratory illness	+
Dandenong arenavirus	454 NGS [70]	Subtraction and BLAST search	Fatal febrile illness in transplant patients	++
Lujo arenavirus	454 NGS [71]	Subtraction and BLAST search	Acute hemorrhagic fever	++
TDAV (Theiler's disease-associated virus), a novel pegivirus	Illumina NGS [73]	BLAST search and <i>de novo</i> genome assembly	Hepatitis (horses)	++
Bat, canine, horse, and rodent hepaciviruses and pegiviruses	454 NGS [74–77]	BLAST search	Respiratory infection (dogs)	–
Canine bocavirus 3	Illumina NGS [78]	BLAST search	Hemorrhagic diarrhea and vasculitis (dog)	–
Snake arenaviruses	Illumina NGS [79]	Subtraction and BLAST search	Inclusion body disease (snakes)	++

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