Commentary

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A Genomics Comparison of Affected Individuals as a Novel Approach to Investigating Pathogenesis of Severe Disease Caused by Dengue Virus Infection

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Abstract

Of the millions of humans infected with the dengue virus worldwide each year a relatively small proportion develop the most severe manifestations of disease, either dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). Nonetheless, as a consequence countless people are debilitated and the global death toll continues to rise annually. By comparing the genomes of individuals who have suffered DHF/DSS with those who have experienced only the more common milder form of disease, dengue fever, differences in genetic predisposition to infection may be revealed. This may be beneficial in two ways. First, if mutations are identified in protein-coding genes, the expressed proteins may be investigated for their putative role in DHS/DSS pathogenesis. This could provide novel targets for anti-viral drug design specifically against DHF/DSS. Second, if several reliable genetic markers were to be uncovered, this would facilitate the rapid identification of patients who are at high risk of suffering DHF/DSS. The routine use in a hospital setting of such a protocol to determine genetic susceptibility could lighten the burden of disease on public health care systems in dengue-endemic regions.

Keywords: Dengue; Virus; Disease; Pathogenesis; Susceptibility; Genome; Genomics

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Introduction

The possible outcomes of dengue virus infection in humans range vastly from asymptomatic cases or those causing mild influenza-like symptoms known as dengue fever, through to severe disease, notably dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). These manifestations lead to metabolically dangerous conditions including increased vascular permeability, hypovolaemia and circulatory failure. The most reliable recent estimate of disease burden is that each year dengue causes an estimated 390 million infections, with 96 million symptomatic cases [1]. This leads directly to at least 500,000 dengue-related hospitalizations annually [2], of which an estimated 22,000 are fatal [3]. These statistics indicate that most people remain unaffected by the virus, while a smaller proportion exhibit extreme symptoms, with a low chance of survival without supportive tertiary care. Currently, it cannot be predicted which individuals will progress from experiencing only dengue fever to suffering life-threatening DHF or DSS. This places a substantial burden on public health service providers, especially referral hospitals in developing countries where dengue is particularly prevalent.

Genome analysis of dengue-infected individuals

Based on the majority of people who remain unaffected by dengue or who suffer only mild symptoms, it is possible that DHF/DSS pathogenesis is triggered by exposure to dengue virus in a minority of humans who carry one or more uncommon detrimental genetic mutations. By comparing the genomes of a cohort of individuals who have suffered DHF/DSS with those of a control group who have contracted dengue fever, variations in gene sequences may be identified as being associated with either protection from or susceptibility to DHF/DSS.

Genetic polymorphisms as known risk factors for dengue pathogenesis

Some genetic risk factors are already known (**Table 1**). These

Table 1 Genetic polymorphisms associated with DHF/DSS.

Gene	Effect of polymorphism on DHF/DSS	Additional genes investigated	Population	Serotype	Reference
TGF- β 1	Increased risk	CTLA-4	Taiwanese	DENV-2	[8]
TNF- α -308 GG	Increased risk	IL-10	Sri Lankan	Unknown	[5]
		TAP			
IL-10	Increased risk	TNF-α	Sri Lankan	Unknown	[5]
		TAP			
TNF-α -308 A	Increased risk	TGF-β1	Venezuelan	Unknown	[6]
		IL-6			
		IL-10			
TNF-α -308 GG	Protective	TGF-β1	Venezuelan	Unknown	[6]
		IL-6			
		IL-10			
HLA-DR4	Protective	HLA-DRB1 alleles	Mexican	Unknown	[9]
TAP2	Increased risk	-	Indian	Unknown	[10]
DC-SIGN	Increased risk	-	Taiwanese	DENV-2	[11]
JAK1	Increased risk	728 SNPs from 56 genes	Brazilian	~80% DENV-3	[4]
Fcγ-RII	Increased risk	IL-4	Vietnamese	Unknown	[12]
		MBL			
		IL-1RA			
VDR	Increased risk	IL-4	Vietnamese	Unknown	[12]
		MLB			
		IL-1RA			

CTLA cytotoxic T-lymphocyte-associated protein; DC-SIGN dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; DENV dengue virus serotype; FcR fragment crystallisable region receptor; HLA-DR human leukocyte antigen D-related; IL interleukin; IL-RA interleukin receptor antagonist; JAK Janus kinase; MBL mannose-binding lectin; SNP single nucleotide polymorphism; TAP transporter associated with antigen processing; TGF transforming growth factor; TNF tumour necrosis factor; VDR vitamin D receptor.

polymorphisms have been identified by selecting only a few genes for investigation in each analysis, with the exception of one study [4], which included 728 single nucleotide polymorphisms (SNPs) from a total of 56 genes. Moreover, discrepancies appear between studies; for example, the tumour necrosis factor (TNF)-α -308 GG polymorphism is associated with an increased risk of severe disease in the Sri Lankan population [5], yet it is found to be protective in a Venezuelan community [6]. This perhaps highlights the importance of identifying multiple gene variations, which together may affect DHF/DSS pathogenesis but alone can generate ambiguous conclusions.

Additionally, for the majority of these published investigations the specific dengue serotype was not known, yet this may be an important factor in determining the pathogenesis of infection. The protein sequence identity shared by the four recognized serotypes, DENV 1-4, ranges from 69% to 78% [7-12], indicating the interaction of each serotype with the human host has the potential to vary slightly. Hence, in respect to dengue serotype an in-depth examination of the human genome is required.

Future Research Opportunities

Depending on available genomic data, any future study to identify novel genomic regions involved in DHF/DSS pathogenesis could investigate either the entire genome or only regions containing SNPs. Either method would provide a more comprehensive view of genetic risk factors than is currently available. In the long term distinguishing a person's comparative susceptibility to infection with different dengue serotypes may be an achievable goal.

Conclusion

Extending our knowledge of the genetic risk factors for DHF/DSS may provide the basis for the development of a protocol to predict patient outcome. Individuals who are at high risk of DHF/DSS may then be prioritized for access to specialized critical care treatment. Furthermore, identifying host proteins involved only in DHF/DSS pathogenesis, as opposed to dengue fever pathogenesis, could extend our knowledge of severe disease progression and guide the design of specific anti-viral drugs to alleviate the life-threatening forms of dengue.

Conflict of Interest

The authors declare that they have no competing issues of interest.

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