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An epidemiological approach to uncover comorbidities as potential risk factors for development of viral haemorrhagic fever

Abstract

Viral haemorrhagic fevers form a distinctive category of illness in humans that is typically, but not definitively, characterized by internal bleeding and fever. Disease manifestations are attributed to an autoimmune disorder that is triggered by prior exposure to one of several RNA viruses. These include such well known viruses as Ebola and Lassa, the associated fevers for which are often lethal, even with medical intervention, to dengue and Zika, which do cause severe complications but that are also often subclinical. Aside from the pressing need to establish precisely the mechanism of VHF pathogenicity, screening of genetic markers for comorbidity, which are in close proximity on the same human chromosome and thus may be inherited together, should help to determine risk factors for unrelated inheritable diseases and metabolic disorders. An exemplar is the autoimmune condition type 1 diabetes, which has been identified as a risk factor for dengue haemorrhagic fever. Any correlations found between VHF and a disease with a known molecular basis, such as type 1 diabetes, may be investigated further by examining genomic regions close to those associated with the identified condition. This may reveal genes which encode proteins that play a putative role in the pathogenesis of VHF.

Keywords: Viral haemorrhagic fever, Virus, disease, Pathogenesis, Susceptibility, Comorbidity, Genome, Genomics

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Abbreviations: HLA, Human Leukocyte Antigen; TAP, Transporter Associated with Antigen Processing; VHF, Viral Haemorrhagic Fever

Introduction

Viral haemorrhagic fever (VHF) is a general term for an illness that is frequently severe and in some cases life-threatening, and is often associated with internal bleeding and fever, symptoms which lend themselves to the condition's name. From the perspective of pathogenesis, it is a human autoimmune disorder that is triggered in a person following their exposure to one of a number of viruses. These belong to five families of enveloped, single-stranded, negative sense RNA viruses: arenaviridae (exemplified by Lassa fever, Junin and Machupo); bunyaviridae (Rift Valley fever, Crimean-Congo and Hantaan haemorrhagic fevers); filoviridae (Ebola and Marburg); flaviviridae (yellow fever, dengue and Zika); and paramyxoviridae (Hendra and Nipah).[1]

People are not the natural reservoir for any of these VHF-causing viruses, which only occasionally break through into the human population when a person comes into contact with an infected primary host, wild animals such as a bat, rats and monkeys, between which it is spread either directly or by biting insects. However, with some viruses, after accidental transmission from the non-human host, persons can transmit the virus to one another.[2] VHF viruses are restricted geographically to regions where their natural host species live, and for most infection of humans is very uncommon.

Clinical cases of VHF in humans for which exposure to these viruses are a trigger occur sporadically and irregularly and so outbreaks cannot be predicted with any certainty. With a few noteworthy exceptions, there is no cure or established drug treatment for VHFs. Currently, cases are diagnosed with a blood test, either by PCR or serology or both, depending on the virus. Due to the highly infectious nature of some viruses, the highest level safety procedures are followed assiduously during collection and transport of specimens, and testing is performed in a public health laboratory under strict biosafety conditions.[3]

There is a drive to understand in more detail the pathogenicity of VHF and how this may be combated.[4] Aside from this immediate focus, the study of VHF may have a supplementary benefit in shedding light on risk factors for diseases and metabolic disorders in humans. This is through genetic screening of markers for comorbidity that are closely associated on the same human chromosome. An epidemiological study is proposed to compare the medical history of individuals who have suffered VHF with a control group of individuals who are known to have been infected with a virus known to cause VHF but who have not suffered clinical manifestations. Such a situation may not arise for the often lethal types of VHF, such as Ebola or Lassa fever, but do so frequently for some others, for instance dengue and Zika, for which infection is often asymptomatic in healthy adults. It is hypothesized that such a comparative analysis may reveal a pattern of comorbidity that indicates a correlation or association between contracting VHF and the development of other apparently unrelated diseases or disorders.

The severe reaction observed in some people infected with a virus may be due to an alteration of normal immune function. The region of the genome which codes for proteins involved in this proposed immune response may, by coincidence, be in close proximity to sequences encoding proteins involved in other diseases or disorders. Hence, these two regions may often be inherited together, which would therefore be revealed by an epidemiological study.

This method may uncover inheritable diseases or disorders which are risk factors for VHF by means of gene linkage. As such, they may

also act as correlates of viral infection. For example, diabetes has been identified as a risk factor for dengue haemorrhagic fever.[5] Expression of genes HLA-DQA1 and HLA-DQB1 has been linked to type 1 diabetes, an autoimmune condition in which the immune system is activated to destroy the beta cells in the pancreas that secrete insulin.[6] As it happens, these genes are located close to TAP1, TAP2 and HLA-DRB1 on chromosome 6, all three of which have been associated with dengue haemorrhagic fever.[7-9] The proximity of these genes is illustrated in Figure 1.

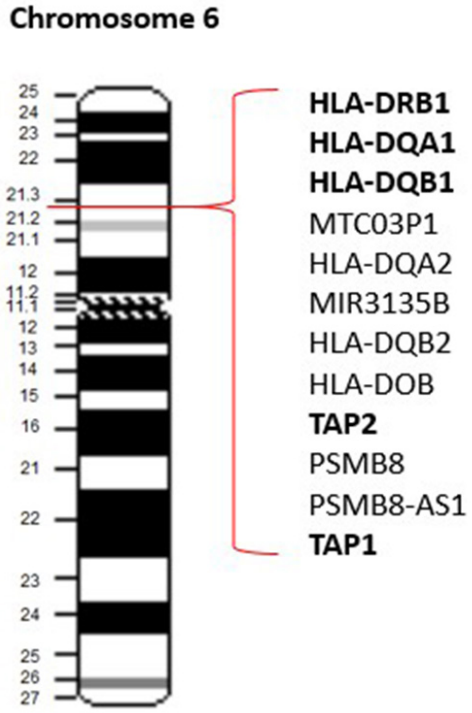

Figure 1 Schematic image of human chromosome 6, showing genes located in the region of 32,561K - 32,916K base pairs. Sourced from NCBI Map Viewer.

Conclusion

Screening for genetic linkage is a powerful tool to aid the identification of risk factors for the coinheritance of unrelated conditions, which thereby act as indirect markers of susceptibility or resistance, in this instance relating to comorbidity for VHF. Any correlations found between VHF and a disease with a known molecular basis, such as that demonstrated for dengue haemorrhagic fever with type 1 diabetes, may be investigated further by examining the regions of the genome close to those associated with the identified disease. This may highlight protein-coding genes that are potentially involved in the pathogenesis of VHF. Large-scale epidemiological cohort studies are warranted.

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Conflicts of interest

None.

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