Applied informatics manipulation for fight against dengue

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Abstract

Dengue is an important tropical infectious disease. This infection has been widely studied and there are many reports on its pre-clinical and clinical aspects. In the era of information technology, scientists can successfully manipulate the large amount of information available on dengue for use in the diagnosis, treatment and control of this disease. In this article, the author briefly summarizes and comments on applied informatics manipulation for the prevention and control of dengue.

Keywords: Dengue; Informatics; Manipulation.

Introduction

Dengue is an important tropical infectious disease that has become a focused disease and its effective control for sustainability requires all-round efforts. There are many research studies on different aspects of this effort: epidemiology, clinical, diagnostics, treatment, and prevention and control of dengue. Various types of dengue researches can be summarized by their characteristics into pre-clinical and clinical studies. For pre-clinical study, scientists usually study the pathophysiology of dengue by standard methods of scientific research. For clinical study, physicians are concerned with diagnosis and therapeutic research on dengue.

Basically, these dengue research areas can be divided into four main groups. The first group relates to descriptive study focusing mainly on the natural history of dengue. The good examples are studies on dengue prevalence and clinical cases summarization. The second group pertains to analytical study. This kind of work focuses mainly on the cause and result to derive odd ratio and risk estimation. The third group of studies focuses on the development of sensitive and dengue-specific diagnostic tests. The last group of work is the experimental group. This mainly focuses on clinical studies for dengue as previously mentioned. This kind of work is considered useful for establishing of real-time clinical practices. However, in addition to these classical approaches, use of database and information technology is important. In the era of information technology, scientists can successfully scan the heap of information available on dengue for usage in diagnosis, treatment and control of the disease. This

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article tries to briefly summarize the application of informatics technology for the development of new technologies/strategies in all aspects of control and management of DF/DHF.

Database searching for natural history study of dengue

As previously mentioned, case summarization is a basic descriptive study for dengue research. In the past, the summarization could be undertaken when there was enough data for analysis. The analysis can be done only if the sample size of the data is sufficient for statistical analysis. However, with advances in database technology, there are numerous databases in medicine, which can serve as primary data source. Of several databases, there is an interesting specific database, DengueInfo, which can be a good gateway to dengue information resources[1]. Many useful data can be freely accessed using this database.

There are many new research studies where scientists have made use of database searching and utilized the same in metanalysis technique to derive the natural history of dengue. The best example is the series of Cochrane Reviews. The paper by Panpanich et al. is within this group[2]. Panpanich et al. carried out metanalysis on the use of corticosteroids for treating dengue shock syndrome (DSS)[2]. In this review, Panpanich et al. searched the Cochrane Infectious Disease Group Specialized Register (January 2006), CENTRAL (The Cochrane Library 2005, Issue 4), MEDLINE (1966 to January 2006), EMBASE (1974 to January 2006), LILACS (1982 to January 2006), and concluded that there was insufficient evidence to confirm the efficacy of the use of corticosteroids in managing dengue shock syndrome[2]. Wiwanitkit recently reported on liver dysfunction due to dengue infection by an analysis of the previously published Thai cases[3]. In this work, Wiwanitkit used Pubmed and Thai Index Medicus database search for deriving primary data to conclude his research results[3]. According to this work, Wiwanitkit noted the importance of detection of abnormal high transaminase enzyme among patients with dengue infection, which consequently developed into hepatic encephalopathy[3]. Wiwanitkit also used a similar technique to summarize the magnitude and pattern of neurological pathology in fatal dengue haemorrhagic fever and found that neurological pathology was also common[4].

Prediction for pathobiology mechanism in dengue

With the advent of computational biology, some new research studies have been carried out on predictive pathobiology of dengue by means of “omics” science. Indeed, there are many newly launched bioinformatics tools that can be applied for dengue research. The basic tools on genomics and proteomics can provide many new data to the scientific community. For example, Wiwanitkit recently explained the pathobiology of DSS by means of predictive bioinformatics. Firstly, Wiwanitkit used phylogenomics analysis to predict the phylogenetic interrelationship and reported that platelet CD61 might have an important role in causing haemorrhagic complication in dengue infection[5]. However, Wiwanitkit further clarified by means of gene ontology that there was no existence of functional similarity between DNS1 and CD61[6]. A study on functional similarity between dengue non-structural protein 1 and platelet integrin/adhesin protein, CD61, showed no confirmative result[6]. Secondly, Wiwanitkit also focused the work on the immune complex generation in dengue. Wiwanitkit successfully demonstrated weak binding affinity of immunoglobin G, which could be an explanation for the immune
mimicking theory in pathophysiological findings in the recovery phase of dengue[7]. The molecular docking technique was mainly used for this predictive-specific study[7]. Wiwanitkit also used the docking study to estimate the size of immune complex and reported its possible relationship to renal pathology in dengue[8]. The author concluded that because entrapment of the immune complex is believed to occur when a previous glomerular lesion causes narrowing of the glomerulus’s diameter, the immune complex should not have a significant role in the pathogenesis of renal failure in dengue infection[8]. Hibberd et al. used a genomics approach to understand the host response during dengue infection and found many new host pathways involved in viral replication in vitro, and also host immune responses that were influenced by viral sequence[9]. For the nature of outbreak, Halide and Ridd recently used a predictive model for describing dengue haemorrhagic fever epidemics[10]. Halide and Ridd also found that the most important determinant in the predictive model was the present number of cases followed by the relative humidity three to four months previously[11].

**In silico mapping of dengue virus epitopes**

Epitope finding is the basic principle in applied immunology. This activity is useful for understanding the immunopathology of infectious diseases as well as to help search for vaccine candidate. In silico mapping of dengue virus epitopes is the current useful application of bioinformatics technology in dengue research. Kutubuddin et al. used basic bioinformatics to describe recognition of CD4(+) T cell epitopes in envelope (E) glycoprotein of Japanese encephalitis, West Nile and dengue viruses[12]. In this work, analysing the occurrence of amphipathic segments, Rothbard-Taylor tetra/pentamer motifs and presence of alpha helix-preferring amino acids were used for epitopes prediction[12]. Wen et al. recently used computational prediction to identify dengue virus-specific CD4(+) T-cell epitopes[13]. According to this work, As a result, C(45-57) (KLMAFIAFLRFL), E(396-408) (SSIGKMFETARG), NS3(23-35) (YRILQRLGLGRSQ), and NS3(141-155) (NREGKIVGLYNGNVV) were the identified epitopes[13]. A similar work was also recently published by Leclerc et al.[14].

**Vaccine search by means of immunomics**

Immunomics is the new specific “omics” science for the study of epitope for production of new vaccines. Immunomics is presently focused on vaccine research. For dengue, the disease without an effective vaccine, immunomics can be useful. In 2007, Khan et al. introduced a systematic bioinformatics approach for the selection of an epitope-based vaccine, targeted to assess its efficacy against dengue[15]. In this study the number of unique protein sequences required to represent complete antigenic diversity of short peptides in dengue virus is significantly smaller than that required to represent complete protein sequence diversity[15]. Recently, in 2008, Khan et al. also published another work on the identification of conservation and variability of dengue virus proteins by mean of bioinformatics[16]. In 2007, Mazumder et al. reported on computational analysis and identification of amino acid sites in dengue E proteins relevant to development of diagnostics and vaccines[17]. They found that six singular sites [N(37), Q(211), D(215), P(217), H(244), K(246)] in dengue E protein that were conserved, were part of the predicted consensus T(h)-cell epitopes and were exposed in the dimer or trimer[17]. They also proposed...
these sites and corresponding epitopic regions as potential candidates for prioritization by experimental biologists for development of dengue vaccines[17].

**Computer-aided drug design**

Computer-aided drug design is another useful bioinformatics application in dengue research. Similar to vaccine search, it is possible to search for a new antiviral compound for dengue based on bioinformatics technology. For example, Zhou et al. recently used virtual screening of small-molecule libraries against dengue virus E protein to identify a new antiviral compound for dengue[18]. According to the study of Zhou et al., P02, a new compound with a change for the development of an effective treatment against dengue virus and related flaviviruses could be identified[18]. Luzhkov et al. used a similar technique, virtual screening and bioassay study, to find new inhibitors for dengue virus mRNA cap (nucleoside-2’O)-methyltransferase[19]. According to this study, a novel inhibitor with a previously unknown scaffold that has an IC(50) value of 60 microM, could be identified[19]. Yang et al. also used combinatorial computational approaches to identify tetracycline derivatives as flavivirus inhibitors[20]. Yang et al. described that rolitetracycline and doxycycline were the two compounds that have their inhibitory effect on dengue virus propagation with IC(50)s estimated to be 67.1 microM and 55.6 microM, respectively[20].

**Plan for dengue control by GIS**

Finally, it should also be noted that not only the information in textual format but also in figure format can be manipulated. The Geographic Information System (GIS) is a good example of figure format data manipulation. There are some recent interesting reports on GIS and dengue. Wiwanitkit reported an observation on the correlation between rainfall and the prevalence of clinical cases of dengue in Thailand[21]. In this work, the collected primary data in general report was used for further manipulation and a predictive map was also generated. A similar work was also reported by Bonet et al. in the Latin America-Caribbean region[22]. In addition, GIS can also be applied for the actual field study data. This is usually used for the vector or mosquito survey. A good example is the paper by Chansand and Kittayapong[23]. According to this work, the immature survey data and the GPS coordinates of house location were combined into GIS maps showing the distribution of immature density and clustering of immature stages and positive containers in the study area[23]. The authors concluded that this approach could be used to improve the efficiency and accuracy of dengue vector surveillance for targeting vector control[23]. Vanwambke et al. concluded that the great variation of determinants for recent dengue infection in space and time should be taken into account when designing local dengue control programmes with the help of GIS[24].

**Diagnosis and prediction of disease outbreaks**

As mentioned before, the bioinformatics technology is useful for the assessment of pathobiology of dengue. The diagnosis and prediction of disease outbreaks can successfully be performed by the bioinformatics technique. Shaw et al. recently used dimension reduction to improve outbreak predictability of multistrain diseases including dengue[25]. Shaw et al. showed that this technique allowed the centre to use manifold equations, which are mainly used for prediction and are applicable even to
noisy systems\textsuperscript{25}. Jackson et al. also proposed a new technique, mass cataloguing, based on mass spectrometry and genotyping, to identify outbreaks of flaviviruses including dengue\textsuperscript{26}. For dengue, the method can help distinguish major subgroupings within each serotype\textsuperscript{26}.

\textbf{Informatics analysis of dengue vector genomes}

Not only the applications for the dengue virus but also for the dengue vector can be performed based on advanced informatics technology. Informatics analysis of dengue vector genomes is presently performed in entomology. For example, Lobo et al. performed analysis of 14 BAC sequences from the \textit{Aedes aegypti} genome\textsuperscript{27}. The data from this study is useful for genome annotation and assembly\textsuperscript{27}. Takahashi et al. used mathematical models for the \textit{Ae. aegypti} dispersal dynamics\textsuperscript{28}. Travelling waves by wing and wind could be identified in this study\textsuperscript{28}.

\textbf{Conclusion}

This paper has tried to review the application of informatics for the diagnosis, treatment and control of dengue virus. As the field of dengue virus research has seen an increased application of informatics over the years, presentation of a review summarizing informatics applications, their impacts and future potentials seems to be in order.

\textbf{References}


