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Title : IDENTIFICATION AND CHARACTERIZATION OF COPY NUMBER VARIATIONS (CNVs) IN DENGUE PATIENTS AND ITS IMPACT WITH VASCULAR LEAKAGE

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Dengue fever is a mosquito-borne tropical disease caused by dengue virus. When infected by any of the four serotypes of dengue viruses, individuals may be asymptomatic or develop a dengue fever. The latter group can progress into severe form of dengue and the etiology of this is still uncertain. This study aims to elucidate copy number variations (CNVs) of the host genes as the factor causing dengue pathogenesis. Blood samples were collected from hospitalized dengue patients and proceeded to DNA extraction. DNA samples (136) were used for genotyping with Human Genome GeneChip 6.0. CNVs were called using Genotyping Console (GTC) 4.1 and Nexus Copy Number 7.0. Results from both algorithms were merged and stringent CNVs were filtered with three public databases; DGV, HapMap3 and SGVP in search for rare case- specific CNVs. Case-specific underlying genes were used in functional analysis with DAVID and IPA to explicate the dengue related biological processes. Significant genes of interest from both softwares were validated using qPCR. Hundred and thirty-six DNA samples from hospitalized dengue patients in four different hospitals were genotyped. A total number of 50,864 (24,806 gains and 26,059 loss) and 34,257 (31,725 gains and 2,534 loss) CNV events were discovered by GTC and Nexus, respectively. After merging, only 3,052 (2,132 gain and 920 loss) stringent CNVs were left. After filtering with public known databases, of the 385 novel rare CNVs, 257 were specific for cases, and 128 were specific for controls, respectively ($p = 0.388$). Six hundred and eighty genes were found underlying the CNVs specific for cases and were eventually loaded into functional analysis softwares. GO terms from unbiased DAVID analysis such as defense response ($p<0.001$; Benjamini corrected $p = 0.034$), inflammatory response ($p<0.001$; Benjamini corrected $p = 0.04$) and response to cytokine stimulus ($p<0.001$; Benjamini corrected $p = 0.038$). From the biased IPA analysis, the candidate genes were clustered into enrichment with antigen presentation pathway as the most significant ($p <0.001$), followed by IL-12 signaling and production in macrophages ($p <0.001$), and interferon signaling ($p <0.001$). Genes from both significant GO terms and pathways; namely *BCKDHB, CTSB, MR1, TAP2, TNFRS1B* and *CXCR4* were considered for validation using qPCR. The 9 out of 10 similarities between SNP 6.0 genotyping and qPCR supported the reliability of this assay. In conclusion, the rare CNVs may be involved in dengue pathogenesis. The rare CNV, which has been reported in other diseases (neuropsychiatric diseases, congenital heart disease and dilated cardiomyopathy), is reported for the first time in infectious diseases.