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Functional *in silico* analysis of ancestry related SNPs associated with classical dengue fever and dengue shock syndrome

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ABSTRACT

Dengue fever is a viral infection caused by one or more of four serotypes of Dengue virus causing a wide spectrum of clinical manifestations that range from mild fever to bleeding and death depending mainly on host genetics. Oliviera et al. have recently reported association of 27 variants as haplotypes with susceptibility to dengue fever and dengue shock syndrome. However; the majority of these variants are non-coding and their functional role is unknown. We analyzed these variants using different bioinformatics tools that predict the regulatory potential of non-coding variants. We found that one third of these variants affect the binding of significant transcription factors involved in the development and regulation of immune related cell lineages and the rest were found to be in strong linkage disequilibrium to the other variants predicted to have regulatory effects. The results of our study can direct future researches towards identifying the exact genomic locations associated with protection against dengue fever infection and possibly the development of new therapeutic treatments.

Keywords: Dengue fever, SNPs, *in silico*, association.

1. INTRODUCTION

Dengue fever is an arthropod-borne viral infection caused by one or more of four serotypes of dengue virus that is transmitted by Aedes mosquitoes (1). The infection causes a wide spectrum of clinical manifestations that range from mild fever and rash to severe bleeding, shock and sometimes death (2). the outcome of dengue viral infection is determined by a complex of interacting factors that include the virus serotype, viral genotype and host genetics (3).

With incidence of 100 million infections per year, dengue fever is considered the most important mosquito borne viral infection in the world (4). Transmission of Dengue fever is widely distributed throughout the world especially in tropical and subtropical regions (4). However not all populations are equally susceptible; East Asian and South American populations are known to be the most susceptible to dengue fever while African populations are known to be more resistant (5,6). This difference in disease susceptibility can be attributed to difference in susceptibility alleles between populations. Ancestry related variants that can infer susceptibility and or resistance to dengue fever have just been discovered. Oliviera et al. have recently reported association of haplotype variants in genes related to inflammation of blood vessels and xenobiotic metabolism with susceptibility of classical dengue fever and dengue

hemorrhagic shock with marked difference in allele frequency between populations (7). However, the majority of these variants are non-coding and their functional role is not yet known. The objective of this article was to analyze these variants using different bioinformatics tools that predict the regulatory mechanism of these variants upon their corresponding genes.

2. MATERIALS AND METHODS

Variants associated with susceptibility or resistance to dengue fever were retrieved from (7). Twenty seven SNPs in 9 genes were reported and the majority of which were intronic, Table 1. The SNPs were analyzed using different bioinformatics tools that predict the functional effect of SNPs on the regulation of corresponding genes. SNPNexus (8), RegulomeDB (9) and SNP Function Prediction (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html) were used to predict the variants' effect on transcription factor binding, miRNA binding and splicing. SIFT (10) and PolyPhen (11) were used to predict the impact of missense SNPs on the structure and function of corresponding proteins. LDlink (12) was used to test for linkage disequilibrium between functional SNPs and those with no predicted function.

Table 1. SNPs, gene, consequences and alleles associated with susceptibility to dengue fever in (7), and analyzed in this study.

SNP	Gene	Consequence	Protective allele	Risk allele
rs2534666	*MICB*	Intronic	G	A
rs2855807	*MICB*	Intronic	T	C
rs3132468	*MICB*	Intronic	T	C
rs3740360	*PLCE1*	Intronic	C	A
rs2274223	*PLCE1*	Intronic	G	A
rs16995800	*PLCB4*	Intronic	G	A
rs2299676	*PLCB4*	Intronic	A	G
rs7269910	*PLCB4*	Intronic	G	A
rs1997696	*PLCB4*	Intronic	A	C
rs6133707	*PLCB4*	Intronic	G	A
rs6056595	*PLCB4*	Intronic	G	A
rs4850931	*CHST10*	Intronic	C	T
rs1030902	*CHST10*	Intronic	T	G
rs2241811	*CHST10*	Intronic	C	T
rs2241810	*CHST10*	Intronic	T	C
rs4149518	*CHST10*	Intronic	A	G
rs2241809	*CHST10*	Intronic	C	T
rs4149510	*CHST10*	Intronic	G	A
rs4851313	*CHST10*	Intronic	G	A
rs3828193	*CHST10*	Coding	G	T
rs6555205	*AHRR*	Intronic	T	C
rs2721020	*AHRR*	Intronic	C	T
rs3829766	*PPP2R5E*	Intronic	A	G
rs6573513	*PPP2R5E*	Intronic	C	T
rs743221	*PPP2R5E*	Intronic	G	A
rs7144210	*PPP2R5E*	Intronic	G	A
rs1480010	*GRIP1*	Intronic	T	C

3. RESULTS AND DISCUSSION

Of 27 SNPs analyzed in this study, 8 were predicted to bind different transcription factors involved in the development and regulation of immune related cell linages. rs3132468 in *MICB* gene and rs6573513 in *PPP2R5E* gene bind CTCF transcription; rs2274223 in *PLCE1* gene binds c-AMP response element binding protein; rs2241811 and rs2241810 in *CHST10* gene bind transcription factor ATF2; rs2241809 in *CHST10* binds two transcription factors ZNF263 and MAFK; rs6555205 in *AHRR* gene binds SPI1. Three SNPs in *PLCB4* gene (rs1997696, rs6133707 and rs6056595) were found to be located in DNAse hypersensitive sites. The SNP rs3828193 in *CHST10* gene is protein coding and was predicted to be deleterious, probably damaging and affecting splicing. For the rest of the variants (15 SNPs) were found to be in strong linkage disequilibrium to the other variants predicted to be regulatory (Figure 1.). The variant rs1480010 in *GRIP1* gene was not predicted to bind any known transcription factor or other regulatory potential.

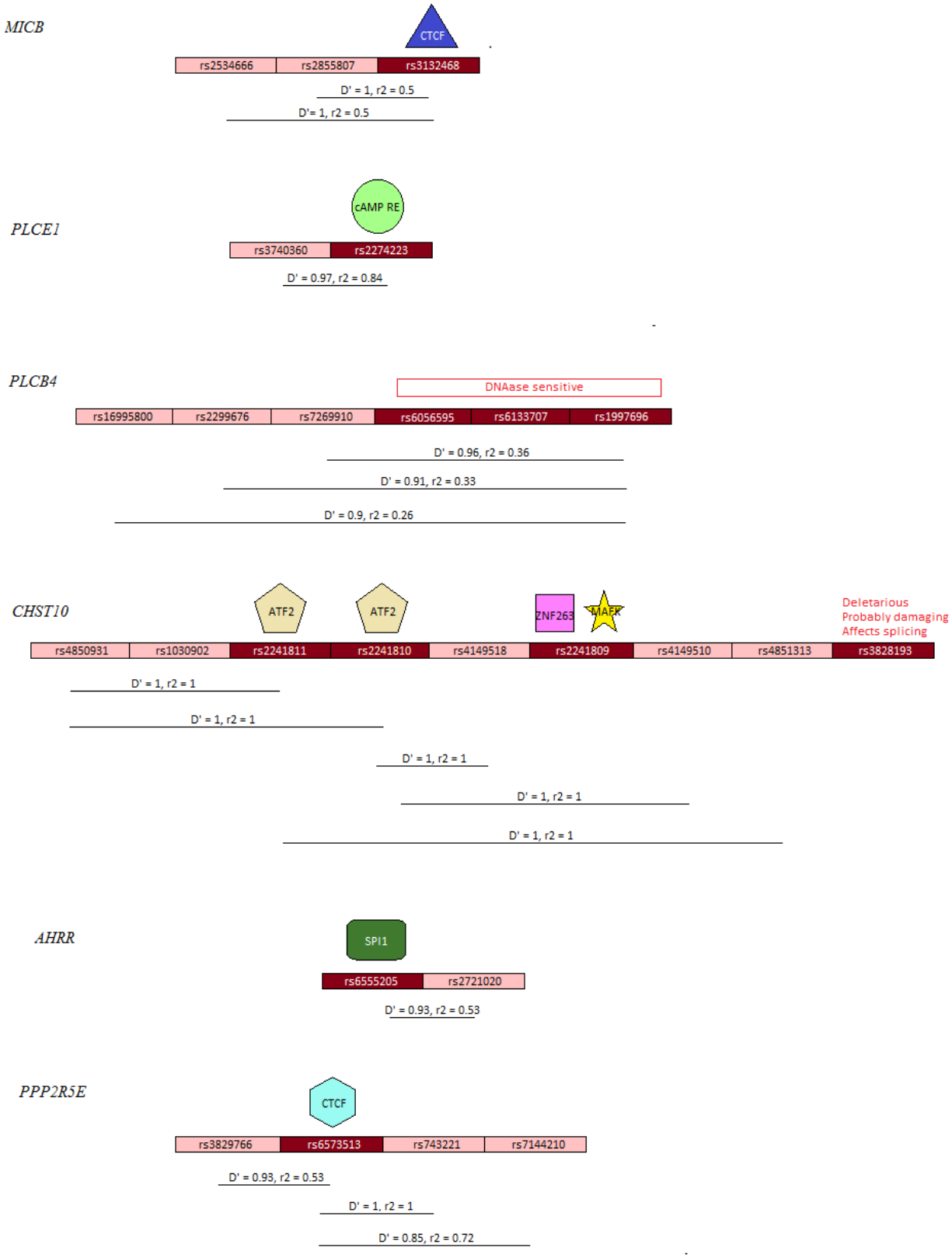

Figure 1. Predicted functional role of SNPs associated with susceptibility to dengue fever from (7).

The current rapidly advancing genome wide association and linkage studies implicated many non-coding SNPs in association to the susceptibility and/or resistance to infectious and non-infectious diseases. However the exact functional roles of many of these variants are yet to be known. In this study we analyzed 27 SNPs previously reported by Oliviera et al. to be associated with susceptibility to classical dengue fever and dengue hemorrhagic shock using different in silico bioinformatics tools that predict the regulatory potential of non-coding variants. We found that one third of these variants affect the binding of transcription factors involved in the development and regulation of immune cells related lineages. Two variants in two different genes bind transcription factor CTCF which critically controls gene expression in macrophages (13), c-AMP response element binding protein and SPI1 affect hematopoiesis and regulate B cells development respectively (14,15), ATF2 regulates T cell proliferation and apoptosis while MAFK is associated with thrombocytopenia (16,17). These results elucidate the functionality of these variants in association to the different phenotypes of dengue fever infection.

For the variants with no prediction of regulatory activity whatsoever, linkage disequilibrium can explain the associations of these variants with susceptibility to dengue fever, since these SNPs were reported in Oliviera et al. as haplotypes and not as individual variants. In our study all variants were in strong linkage disequilibrium with other SNPs predicted to be regulatory for the populations studied by Oliviera et al. (South East Asians and Vietnamese). This result is in accordance with a study by Schaub et al. which found that the majority of SNPs associated with regulatory information are part of a larger region of linkage disequilibrium (18).

The results of our study can direct future researches towards identifying the exact genomic locations associated with protection against dengue fever infection and possibly the development of new therapeutic treatments.

Availability of data and materials:
All data can be made available by the corresponding author upon reasonable request.

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