Population genetic study of variants of genes conferring resistance to severe dengue disease
## Flaviviridae

<table>
<thead>
<tr>
<th>Virus</th>
<th>Serocomplex</th>
<th>Clade</th>
<th>Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>West Nile</td>
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<tr>
<td>Kunjin</td>
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<tr>
<td>Japanese encephalitis</td>
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<td>Murray Valley encephalitis</td>
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<td>St Louis encephalitis</td>
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<tr>
<td>Dengue-1</td>
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<tr>
<td>Dengue-3</td>
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<td>Dengue-2</td>
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<td>Dengue-4</td>
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<tr>
<td>Yellow fever</td>
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<tr>
<td>Central European encephalitis</td>
<td>Tick-borne encephalitis</td>
<td>IV</td>
<td>Tick-borne</td>
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<td>Far Eastern encephalitis</td>
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<td>Powassan</td>
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<tr>
<td>Dakar bat</td>
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</tbody>
</table>

*Clade numbers and clusters indicated in the diagram.*
Manifestations of the dengue syndrome

Dengue virus infection

- Asymptomatic
  - Fever
    - Undifferentiated Fever UF
    - Symptomatic
      + Hemorrhagic tendency
        - Plasma leakage
          - Dengue fever Syndrome DF
          - Dengue hemorrhagic fever DHF
          + Dengue shock Syndrome DSS

Symptom severity

Rare manifestations: Encephalitis, Hepatitis
Emergence of Dengue Disease World-wide

Countries reported DF/DHF

<1960: ▼

>1960: ▲
World wide dengue disease severity difference
A complex interplay between human-virus-vector and environment
Evidence of human genetic factors in severity of dengue disease

Dengue viruses cause clinical manifestations in only a small percentage of infected individuals

- Caucasian > African/ Chinese > Malasian
- HLA-A and B association study
- Others studies
  - FCGR IIA
  - TNFα
Early innate immune recognition of dengue virus
Immature DCs that express the C-lectin DC-SIGN support DEN virus replication

DEN virus-infected MDDC<sup>DC-SIGN+</sup> (IF assay using anti-DEN Abs)

Patients

Inclusion criteria

Dengue cases

Fever + hemorrhagic tendency: eg petechii or rashes or hepatomegaly

+ serological diagnosis: paired serum

Evidence of plasma leakage

democoncentration or pleural effusion

DF Group

DHF/DSS Group

Age 5-15 year-old

Control Group

blood donors from the same ethnic background
DC-SIGN-336 association study

Frequency of DC-SIGN-336 genotype G/G and G/A

<table>
<thead>
<tr>
<th>Location</th>
<th>Controls</th>
<th>DF</th>
<th>DHF/DSS</th>
<th>OR</th>
<th>(95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rama</td>
<td>296</td>
<td>52</td>
<td>183</td>
<td>14.31</td>
<td>(3.34-61.23)</td>
<td>2.3 x10^-4</td>
</tr>
<tr>
<td>Siriraj</td>
<td>216</td>
<td>73</td>
<td>168</td>
<td>3.79</td>
<td>(1.62-8.87)</td>
<td>0.0024</td>
</tr>
<tr>
<td>Khonkaen</td>
<td>184</td>
<td>27</td>
<td>103</td>
<td>99.75</td>
<td>(12.70-783.54)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Sakuntabhai, et al.  
Nat Genet 2005
The A to G change in -336 affects the promoter activity of [-472;-1]$^{CD209}$ in human myeloid cells.

P. Despres
DEN virus infection correlates with the level of DC-SIGN expression

(Lozach et al., J.Biol.Chem. 280: 23698, 2005)
Allelic distribution of DC-SIGN-336G in different populations

%  RARE  MILD/MODERATE  MOST SEVERE

Zimbabwean  Sub-saharan African  South African Coloured  Caucasian Canadian  Caucasian European  Thai  Asian

DC-SIGN-336G -DF protective allele

Boily-Larouche et al. 2007
Gene encoding the 1b isoform of 2’-5’ Oligo adenylate synthetase

Sensitive strains

Resistant strains

Genetic susceptibility to West Nile (WN) virus in the mouse model

Mashimo et al., PNAS 2003
The IFN-inducible OAS/RNase L system is involved in the innate antiviral immunity to RNA viruses.
Cluster of genes encoding mouse 2'-5' Oas proteins

Mouse Oas gene cluster

RPCI-23-39M18

Cen. 30 Kbp Tel.

Dtx1

Oas2
(Oasl11)

Oas3
(Oasl10)

Iap

Oas1e Oas1c Oas1b

Oas1f Oas1h Oas1g Oas1a Oas1d

Rph3a

8 tandemly arranged transcription units for Oas1

Human OAS gene cluster

(http://genome.ucsc.edu)
OAS3-S381R vs DEN severity

Control
- CC: 506
- CG: 176
- GG: 12

DF
- CC: 174
- CG: 72
- GG: 6

DHF
- CC: 323
- CG: 128
- GG: 7

DSS
- CC: 121
- CG: 24
- GG: 2

Graphs by finaldx4
Allelic distribution of OAS3-S381R-G in different populations

Thai

Caucasian

East Asian

African

www.hapmap.org
Summary:

Genetic study of human response to infection

- Help understanding human-pathogen interaction

- Direct benefit: to identify a person susceptible to severe infection >> prevention and early treatment

- Identify new drug target or new treatment strategy

- Less social impact than mutations of genetic diseases or chronic diseases
Perspectives

- World wide scale clinical/viral/environmental/genetics study
- Genome scan association study
World wide scale
clinical/environmental/genetics study of
Arboviruses
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Génétique, Papillomavirus et Cancer Humain
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“The Thailand SNP discovery program”
**BIOTEC, National Science and Technology Development Agency NSTDA, Thailand**