

# Genetic Association Studies of *MICB* and *PLCE1* with Severity of Dengue in Indonesian and Taiwanese Populations

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Table S1. Baseline characteristics of the Taiwanese population

| Characteristic   | Number of subjects  |                     | <i>p value</i>   |
|--|---------------------|---------------------|------------------|
|  | DF ( <i>N</i> =238) | DHF ( <i>N</i> =35) |                  |
| Age (mean ± SD, years)                                   | 47.97 ± 17.09       | 66.97 ± 13.09       | <b>&lt;.0001</b> |
| Male gender (%)  | 128 (53.78)         | 17 (48.57)          | 0.332            |
| Female gender (%)  | 110 (46.22)         | 18 (51.43)          |                  |
| Platelets (mean ± SD, 10 <sup>3</sup> /mm <sup>3</sup> ) | 145.34 ± 66.73      | 96.97 ± 73.44       | <b>0.0005</b>    |

Abbreviations: DF, dengue fever; DHF, dengue hemorrhagic fever; SD, standard deviation

Table S2. Baseline characteristics of the Indonesian population

| Characteristic   | Number of subjects  |                     |                     | <i>p</i> value |               |              |
|--|---------------------|---------------------|---------------------|----------------|---------------|--------------|
|  | DF ( <i>N</i> = 67) | DHF ( <i>N</i> =83) | DSS ( <i>N</i> =10) | DF vs DHF      | DF vs DSS     | DHF vs DSS   |
| Age (mean ± SD, years)                                   | 19.07 ± 15.63       | 16.28 ± 14.07       | 10.05 ± 5.93        | 0.204          | 0.078         | 0.261        |
| Male gender (%)  | 37 (55.22)          | 50 (60.24)          | 6 (60)              | 0.536          | 1.000         | 1.000        |
| Female gender (%)  | 30 (44.78)          | 33 (39.76)          | 4 (40)              |                |               |              |
| Length of hospitalization (mean ± SD, day)               | 4.1 ± 1.18          | 4.39 ± 1.40         | 4.40 ± 0.97         | 0.318          | 0.401         | 0.828        |
| Secondary infection (%)                                  | 36 (53.73)          | 57 (68.67)          | 7 (70)              | 0.060          | 0.498         | 1.000        |
| Days of illness (mean ± SD, day)                         | 3.97 ± 1.59         | 3.93 ± 1.54         | 3.80 ± 1.23         | 0.993          | 0.957         | 0.954        |
| Platelets (mean ± SD, 10 <sup>3</sup> /mm <sup>3</sup> ) | 137.69 ± 78.61      | 103.79 ± 47.74      | 64.1 ± 23.62        | <b>0.007</b>   | <b>0.0004</b> | <b>0.004</b> |
| Hematocrit (mean ± SD, %)                                | 40.90 ± 5.83        | 41.40 ± 5.62        | 43.68 ± 5.62        | 0.753          | 0.165         | 0.297        |

Abbreviations: DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; SD, standard deviation

Table S3. Hematological values of Indonesian population

| Variables (units)              | N   | Mean of variables $\pm$ SD |                     |                     |                     | <i>p</i> value |           |            |
|--------------------------------|-----|----------------------------|---------------------|---------------------|---------------------|----------------|-----------|------------|
|                                |     | All dengue                 | DF                  | DHF                 | DSS                 | DF vs DHF      | DF vs DSS | DHF vs DSS |
| Leucocytes (/mm <sup>3</sup> ) | 140 | 4760 $\pm$ 4690            | 4560 $\pm$ 2830     | 4780 $\pm$ 5900     | 5710 $\pm$ 3000     | 0.533          | 0.173     | 0.072      |
| Hemoglobin (g/dL)              | 142 | 13.94 $\pm$ 2.27           | 13.97 $\pm$ 2.18    | 13.82 $\pm$ 2.38    | 14.67 $\pm$ 1.92    | 0.553          | 0.307     | 0.214      |
| ALT (U/L)                      | 32  | 102.68 $\pm$ 120.35        | 83.26 $\pm$ 68.41   | 106.16 $\pm$ 131.76 | 279.50 $\pm$ 365.57 | 0.982          | 0.954     | 0.914      |
| AST (U/L)                      | 32  | 165.24 $\pm$ 218.70        | 143.81 $\pm$ 187.92 | 162.88 $\pm$ 230.77 | 391.40 $\pm$ 470.08 | 0.613          | 0.775     | 0.591      |
| Blood glucose (mg/dL)          | 55  | 118.49 $\pm$ 48.80         | 125.82 $\pm$ 64.15  | 108.22 $\pm$ 22.47  | 126.20 $\pm$ 39.65  | 0.704          | 0.659     | 0.352      |

SD: standard deviation; DF: dengue fever; DHF: dengue hemorrhagic fever; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Table S4. Association analysis between *MICB* and *PLCE1* single nucleotide polymorphisms (SNP)s and platelet count of Indonesian population (n=160)

| Gene Variant              | Genotype | Platelet count (10 <sup>3</sup> /mm <sup>3</sup> ) |           | Genotypic<br><i>p</i> value | Dominant<br><i>p</i> value | Recessive<br><i>p</i> value | Log-Additive<br><i>p</i> value |
|---------------------------|----------|--|-----------|-----------------------------|----------------------------|-----------------------------|--------------------------------|
|                           |          | ≤ 100 (%)  | > 100 (%) |                             |                            |                             |                                |
| <i>MICB</i><br>rs3132468  | CC       | 9 (7.3)  | 2 (5.6)   | 0.649                       | 0.355                      | 0.716                       | 0.371                          |
|                           | CT       | 50 (40.3)  | 12 (33.3) |                             |                            |                             |                                |
|                           | TT       | 65 (52.4)  | 22 (61.1) |                             |                            |                             |                                |
| <i>PLCE1</i><br>rs3765524 | CC       | 46 (37.1)  | 11 (30.6) | 0.753                       | 0.467                      | 0.978                       | 0.596                          |
|                           | CT       | 61 (49.2)  | 20 (55.6) |                             |                            |                             |                                |
|                           | TT       | 17 (13.7)  | 5 (13.9)  |                             |                            |                             |                                |
| <i>PLCE1</i><br>rs3740360 | AA       | 54 (43.5)  | 11 (30.6) | 0.364                       | 0.157                      | 0.803                       | 0.238                          |
|                           | AC       | 58 (46.8)  | 21 (58.3) |                             |                            |                             |                                |
|                           | CC       | 12 (9.7)   | 4 (11.1)  |                             |                            |                             |                                |

Table S5. Association analysis between *MICB* and *PLCE1* single nucleotide polymorphisms (SNP)s and platelet count of Taiwanese Population (n=271)

| Gene Variant              | Genotype | Platelet count ( $10^3/\text{mm}^3$ ) |             | Genotypic      | Dominant       | Recessive      | Log-Additive   |
|---------------------------|----------|---------------------------------------|-------------|----------------|----------------|----------------|----------------|
|                           |          | $\leq 100$ (%)                        | $> 100$ (%) | <i>p</i> value | <i>p</i> value | <i>p</i> value | <i>p</i> value |
| <i>MICB</i><br>rs3132468  | CC       | 1 (1.4)                               | 0           | 0.359          | 0.986          | 0.269          | 0.358          |
|                           | CT       | 10 (13.7)                             | 30 (15.2)   |                |                |                |                |
|                           | TT       | 62 (84.9)                             | 168 (84.8)  |                |                |                |                |
| <i>PLCE1</i><br>rs3765524 | CC       | 52 (71.2)                             | 127 (64.1)  | 0.543          | 0.269          | 0.744          | 0.302          |
|                           | CT       | 18 (24.7)                             | 61 (30.8)   |                |                |                |                |
|                           | TT       | 3 (4.1)                               | 10 (5.1)    |                |                |                |                |
| <i>PLCE1</i><br>rs3740360 | AA       | 53 (72.6)                             | 132 (66.7)  | 0.532          | 0.347          | 0.415          | 0.285          |
|                           | AC       | 19 (26.0)                             | 60 (30.3)   |                |                |                |                |
|                           | CC       | 1 (1.4)                               | 6 (3.0)     |                |                |                |                |

Table S6. Association of *MICB* rs3132468, *PLCE1* rs3765524, *PLCE1* rs3740360 and dengue severity in patients with primary dengue infection in Indonesian population

| Genotype               | Number of subjects ( <i>N</i> =60) |           |          | DF vs DHF |          |           |              | DF vs DSS |          |           |              | DHF vs DSS |          |           |              |
|------------------------|------------------------------------|-----------|----------|-----------|----------|-----------|--------------|-----------|----------|-----------|--------------|------------|----------|-----------|--------------|
|                        | DF (%)                             | DHF (%)   | DSS (%)  | Genotypic | Dominant | Recessive | Log-Additive | Genotypic | Dominant | Recessive | Log-Additive | Genotypic  | Dominant | Recessive | Log-Additive |
| <i>MICB</i> rs3132468  |                                    |           |          |           |          |           |              |           |          |           |              |            |          |           |              |
| T/T                    | 18 (58.1)                          | 14 (53.8) | 1 (33.3) |           |          |           |              |           |          |           |              |            |          |           |              |
| C/T                    | 12 (38.7)                          | 11 (42.3) | 1 (33.3) | 0.948     | 0.749    | 0.899     | 0.747        | 0.267     | 0.410    | 0.109     | 0.156        | 0.318      | 0.497    | 0.132     | 0.203        |
| C/C                    | 1 (3.2)                            | 1 (3.8)   | 1 (33.3) |           |          |           |              |           |          |           |              |            |          |           |              |
| <i>PLCE1</i> rs3765524 |                                    |           |          |           |          |           |              |           |          |           |              |            |          |           |              |
| C/C                    | 9 (29.0)                           | 10 (38.5) | 1 (33.3) |           |          |           |              |           |          |           |              |            |          |           |              |
| C/T                    | 17 (54.8)                          | 15 (57.7) | 2 (66.7) | 0.265     | 0.452    | 0.114     | 0.186        | 1.000     | 0.877    | 1.000     | 1.000        | 1.000      | 0.861    | 1.000     | 1.000        |
| T/T                    | 5 (16.1)                           | 1 (3.8)   | 0        |           |          |           |              |           |          |           |              |            |          |           |              |
| <i>PLCE1</i> rs3740360 |                                    |           |          |           |          |           |              |           |          |           |              |            |          |           |              |
| A/A                    | 9 (29.0)                           | 11 (42.3) | 1 (33.3) |           |          |           |              |           |          |           |              |            |          |           |              |
| A/C                    | 17 (54.8)                          | 14 (53.8) | 2 (66.7) | 0.227     | 0.295    | 0.114     | 0.123        | 1.000     | 0.877    | 1.000     | 1.000        | 1.000      | 0.762    | 1.000     | 1.000        |
| C/C                    | 5 (16.1)                           | 1 (3.8)   | 0        |           |          |           |              |           |          |           |              |            |          |           |              |

DF: Dengue Fever; DHF: Dengue Hemorrhagic Fever; DSS : Dengue Shock Syndrome

Table S7. Association of *MICB* rs3132468, *PLCE1* rs3765524, *PLCE1* rs3740360 and dengue severity in Indonesian population

| Genotype        | Number of subjects (N=160) |           |         | DF vs DHF |          |           | DF vs DSS |          |           | DHF vs DSS |          |           |              |
|-----------------|----------------------------|-----------|---------|-----------|----------|-----------|-----------|----------|-----------|------------|----------|-----------|--------------|
|                 | DF (%)                     | DHF (%)   | DSS (%) | Genotypic | Dominant | Recessive | Genotypic | Dominant | Recessive | Genotypic  | Dominant | Recessive | Log-additive |
| MICB rs3132468  |                            |           |         |           |          |           |           |          |           |            |          |           |              |
| T/T             | 40 (59.7)                  | 44 (53)   | 3 (30)  |           |          |           |           |          |           |            |          |           |              |
| C/T             | 24 (35.8)                  | 33 (39.8) | 5 (50)  | 0.629     | 0.411    | 0.475     | 0.115     | 0.076    | 0.113     | 0.275      | 0.164    | 0.228     | 0.108        |
| C/C             | 3 (4.5)                    | 6 (7.2)   | 2 (20)  |           |          |           |           |          |           |            |          |           |              |
| PLCE1 rs3765524 |                            |           |         |           |          |           |           |          |           |            |          |           |              |
| C/C             | 25 (37.3)                  | 27 (32.5) | 5 (50)  |           |          |           |           |          |           |            |          |           |              |
| C/T             | 33 (49.3)                  | 43 (51.8) | 5 (50)  | 0.811     | 0.540    | 0.700     | 0.506     | 0.447    | 0.595     | 0.373      | 0.282    | 0.347     | 0.373        |
| T/T             | 9 (13.4)                   | 13 (15.7) | 0       |           |          |           |           |          |           |            |          |           |              |
| PLCE1 rs3740360 |                            |           |         |           |          |           |           |          |           |            |          |           |              |
| A/A             | 29 (43.3)                  | 30 (36.1) | 6 (60)  |           |          |           |           |          |           |            |          |           |              |
| A/C             | 31 (46.3)                  | 44 (53)   | 4 (40)  | 0.662     | 0.373    | 0.937     | 0.687     | 0.322    | 0.585     | 0.316      | 0.149    | 0.589     | 0.316        |
| C/C             | 7 (10.4)                   | 9 (10.8)  | 0       |           |          |           |           |          |           |            |          |           |              |

DF: dengue fever; DHF: dengue hemorrhagic fever; DSS: dengue shock syndrome

Table S8. Association of *MICB* rs3132468, *PLCE1* rs3765524, *PLCE1* rs3740360 and dengue severity in Taiwanese population

| Genotype  | Number of subjects (N=273) |           | DF vs DHF |          |           |
|---|----------------------------|-----------|-----------|----------|-----------|
|   | DF (%)                     | DHF (%)   | Genotypic | Dominant | Recessive |
| MICB rs3132468  |                            |           |           |          |           |
| T/T   | 201 (84.5)                 | 31 (88.6) | 0.824     | 0.511    | 1.000     |
| C/T   | 36 (15.1)                  | 4 (11.4)  |           |          |           |
| C/C   | 1 (0.4)                    | 0         |           |          |           |
| PLCE1 rs3765524   |                            |           |           |          |           |
| C/C   | 160 (67.2)                 | 19 (54.3) | 0.194     | 0.139    | 0.545     |
| C/T   | 66 (27.7)                  | 15 (42.9) |           |          |           |
| T/T   | 12 (5)                     | 1 (2.9)   |           |          |           |
| PLCE1 rs3740360   |                            |           |           |          |           |
| A/A   | 164 (68.9)                 | 21 (60)   | 0.297     | 0.299    | 0.600     |
| A/C   | 67 (28.2)                  | 14 (40)   |           |          |           |
| C/C   | 7 (2.9)                    | 0         |           |          |           |
| DF: dengue fever; DHF: dengue hemorrhagic fever; DSS: dengue shock syndrome |                            |           |           |          |           |