Genetic variants of glutamate receptor gene family in Taiwanese Kawasaki disease children with coronary artery aneurysms

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Abstract

Background: Patients with Kawasaki disease (KD), a pediatric systemic vasculitis, may develop coronary artery aneurysm (CAA) as a complication. To investigate the role of glutamate receptors in KD and its CAA development, we performed genetic association studies.

Methods and results: We examined the whole family of glutamate receptors by genetic association studies in a Taiwanese cohort of 262 KD patients. We identified glutamate receptor ionotropic, kainate 1 (GRIK1) as a novel susceptibility locus associated with CAA formation in KD. Statistically significant differences were noted for factors like fever duration, 1st Intravenous immunoglobulin (IVIG) used time (number of days after the first day of fever) and the GRIK1 (rs466013, rs425507, and rs38700) genetic variants. This significant association persisted even after using multivariate regression analysis (Full model: for rs466013: odds ratio =2.12; 95% CI =1.22-3.65; for rs425507: odds ratio =2.16; 95% CI =1.26-3.76; for rs388700: odds ratio =2.16; 95% CI =1.26-3.76).

Conclusions: We demonstrated that GRIK1 polymorphisms are associated CAA formation in KD, even when adjusted for fever duration and IVIG used time, and may also serve as a genetic marker for the CAA formation in KD.

Keywords: KD, GRIK1, Single nucleotide polymorphism, CAA

Background

Patients with Kawasaki disease (KD), an acute systemic vasculitis, may develop coronary artery aneurysm (CAA) as a complication. KD is one of the leading causes of acquired cardiovascular diseases in childhood. Infectious agents, host immune dysregulation, and genetic susceptibility are thought to be responsible for the development of KD and its related complications [1-3]. However, the pathological mechanisms underlying KD remain to be elucidated.

Numerous genome-wide association studies have been conducted to identify host cellular genes that affect KD susceptibility [4-14] in the European, Japanese, Korean, and Taiwanese populations. In the European population [11,13], no common SNPs have been identified as susceptibility loci for European KD. However, a common SNP (rs2233152; MIA gene) was observed in the European, Japanese, and Taiwanese populations [9-11]. Common gene SNPs among Asians including Japanese, Taiwanese, and Korean populations have also been observed [4,6,9,10,12,14,15]. Six SNPs, namely, rs2736340 (BLK), rs2618479 (BLK), rs6993775 (BLK), rs10401344 (ITPKC), rs2233152 (MIA), and rs4813003 (CD40) have been observed in both Japanese and Taiwanese populations [9,10] (Additional files 1 and 2). These studies suggest that genes involved in the immune-regulatory responses and cardiovascular-related pathogenesis may contribute to KD susceptibility.

Glutamate receptors were initially demonstrated to play important roles in excitatory neurotransmission in the brain and interneuronal communication [16]. Based on their different activation mechanisms, glutamate receptors...
Genetic association study of the glutamate receptor gene family in Taiwanese KD children and controls

To identify KD susceptibility genes, a total of 53 SNPs of 16 genes within the glutamate receptor gene family including GRIK1, GRIK2, GRIK3, GRIK4, GRIK5, GRIA1, GRIA2, GRIA4, GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, and GRM8 genes were genotyped in 262 Taiwanese KD children and in 1107 healthy people from the general population of Taiwan who were Han Chinese ethnic background for the SNP association study (Table 1). No significant differences were found between these 2 groups, suggesting that the glutamate receptor family genes may not contribute to KD susceptibility.

**GIKI1 genetic polymorphisms may be related to KD-associated CAA complications**

To examine the role of glutamate receptors in KD-associated CAA complications, we analyzed the correlation between KD children and the whole glutamate gene family. As shown in Table 2, the genotype distributions (dominant model) of 6 glutamate gene SNPs were statistically different between these 2 groups (p<0.05). These SNPs were rs466013, rs425507, rs388700, rs402280, rs17104835 and rs712723. Among these, 4 SNPs were found to be located in the GRIK1 gene (p=0.007, 0.005, 0.004 and 0.022, respectively) (Additional file 1). GRIK1 consists of 18 exons and is located at 21q21.3 as shown in Figure 1. All SNPs were in Hardy-Weinberg equilibrium and had a successful genotyping frequency of >99%. The linkage disequilibrium (LD) structure of this region was also established, with 1 haplotype block determined. Four SNPs were located in that block. To evaluate the relationship among these 4 SNPs, pairwise LD analysis was performed. The D’ statistics were all 1.0. Strong LD was observed in the following 2 groups of SNPs, group1 (rs466013, rs425507, rs388700), with the r² statistics >0.5 between every 2 SNPs in each group (data not shown). The frequencies of the TT and TC genotypes of GRIK1 (rs466013) were significantly higher in KD patients with CAA than those in patients without CAA (63.2% for KD with CAA and 44.9% for KD without CAA complications; odds ratio =2.11 [95% confidence interval (CI) =1.22-3.65]). Similar results were also observed in rs425507, rs388700 and rs402280. These data suggest that GRIK1 may be a potential susceptibility locus involved in the development of KD with CAA complications.

**Multivariate regression analyses shows that GRIK1 genetic polymorphisms may be related to CAA formation in KD**

According to the above results, statistically significant differences in factors associated with CAA formation in KD were noted for the clinical characteristics including fever duration (p<0.0001), first IVIG used time (p<0.0001; number of days after the first day of fever), and the GRIK1 (rs466013, rs425507, rs38700, and rs402280) genetic variants (p =0.007, p =0.005, p =0.004, and p =0.022, respectively) (Tables 1 and 3). To further confirm the genetic role of GRIK1, we used multivariate regression analyses to adjust those potential factors (i.e., fever duration and IVIG used time) that may affect the analysis. As shown in Table 3, significant associations between KD with CAA...
| SNP          | Chromosome | Cytoband | Physical position | Nearest genes | Controls No. (%) | KD patients No. (%) | p value | Odds ratio (95% CI) |
|--------------|------------|----------|------------------|---------------|------------------|---------------------|---------|---------------------|
| rs466013     | 21         | q21.3    | 29826300         | GRIK1         | TT + TC 507 (45.9) | 131 (50.2)           | 0.205   | 1.19 (0.91-1.56)    |
|              |            |          |                  |               | CC 599 (54.1)     | 130 (49.8)           |         |                     |
| rs425507     | 21         | q21.3    | 29827658         | GRIK1         | TT + GA 507 (45.8) | 130 (49.6)           | 0.265   | 1.17 (0.89-1.53)    |
|              |            |          |                  |               | AA 600 (54.2)     | 132 (50.4)           |         |                     |
| rs388700     | 21         | q21.3    | 29830158         | GRIK1         | TT + TA 506 (45.7) | 130 (49.6)           | 0.254   | 1.17 (0.89-1.53)    |
|              |            |          |                  |               | AA 601 (54.3)     | 132 (50.4)           |         |                     |
| rs402280     | 21         | q21.3    | 29835401         | GRIK1         | TT + TA 424 (38.3) | 116 (44.3)           | 0.075   | 1.28 (0.97-1.68)    |
|              |            |          |                  |               | AA 683 (61.7)     | 146 (55.7)           |         |                     |
| rs17816480   | 6          | q16.3    | 101522140        | GRIK2         | TT + TC 201 (18.2) | 48 (18.3)            | 0.951   | 1.01 (0.71-1.43)    |
|              |            |          |                  |               | CC 906 (81.8)     | 214 (81.7)           |         |                     |
| rs2786239    | 6          | q16.3    | 101637565        | GRIK2         | GG + GA 186 (16.8)| 45 (17.2)            | 0.677   | 1.06 (0.80-1.41)    |
|              |            |          |                  |               | AA 921 (83.2)     | 217 (82.8)           |         |                     |
| rs4840194    | 6          | q16.3    | 101768497        | GRIK2         | CC + CT 357 (32.2)| 88 (33.6)            | 0.468   | 0.91 (0.69-1.91)    |
|              |            |          |                  |               | TT 750 (67.8)     | 174 (66.4)           |         |                     |
| rs1310715    | 6          | q16.3    | 101961427        | GRIK2         | TT + TC 597 (53)  | 133 (50.9)           | 0.91    | 1.60 (0.80-1.41)    |
|              |            |          |                  |               | CC 520 (47.0)     | 128 (49.1)           |         |                     |
| rs527631     | 1          | p34.3    | 36844396         | GRIK3         | AA + AG 172 (15.5)| 45 (17.6)            | 0.407   | 1.16 (0.81-1.67)    |
|              |            |          |                  |               | GG 935 (84.5)     | 210 (82.4)           |         |                     |
| rs476894     | 1          | p34.3    | 36868682         | GRIK3         | CC + GA 234 (21.1) | 63 (24.0)            | 0.305   | 1.18 (0.86-1.62)    |
|              |            |          |                  |               | AA 873 (78.9)     | 199 (76.0)           |         |                     |
| rs541671     | 1          | p34.3    | 36905238         | GRIK3         | TT + TA 267 (24.1)| 65 (25.9)            | 0.554   | 1.10 (0.80-1.51)    |
|              |            |          |                  |               | AA 840 (75.9)     | 186 (74.1)           |         |                     |
| rs35317705   | 1          | p34.3    | 36972969         | GRIK3         | CC + CT 128 (11.6)| 33 (12.6)            | 0.641   | 1.10 (0.73-1.66)    |
|              |            |          |                  |               | TT 979 (88.4)     | 229 (87.4)           |         |                     |
| rs11218005   | 11         | q23.3    | 120782227        | GRIK4         | AA + AC 132 (11.9)| 35 (13.4)            | 0.523   | 1.14 (0.76-1.70)    |
|              |            |          |                  |               | CC 975 (88.1)     | 227 (86.6)           |         |                     |
| rs3901285    | 11         | q23.3    | 120862726        | GRIK4         | TT + TC 650 (58.7)| 158 (60.3)           | 0.638   | 1.07 (0.81-1.41)    |
|              |            |          |                  |               | CC 457 (41.3)     | 104 (39.7)           |         |                     |
| rs4936566    | 11         | q23.3    | 120944529        | GRIK4         | AA + AG 669 (60.4)| 145 (55.3)           | 0.131   | 0.81 (0.62-1.06)    |
|              |            |          |                  |               | GG 438 (39.6)     | 117 (44.7)           |         |                     |
| rs443239     | 19         | q13.2    | 42001892         | GRIK5         | CC + CG 289 (26.1)| 64 (24.4)            | 0.576   | 0.91 (0.67-1.25)    |
|              |            |          |                  |               | GG 818 (73.9)     | 198 (75.6)           |         |                     |
| rs1493395    | 5          | q33.2    | 153532297        | GRIA1         | AA + AG 565 (51.1)| 125 (47.7)           | 0.326   | 0.87 (0.67-1.14)    |
|              |            |          |                  |               | GG 541 (48.9)     | 137 (52.3)           |         |                     |
| rs12153489   | 5          | q33.2    | 153568777        | GRIA1         | CC + CT 1087 (98.2)| 259 (98.9)           | 0.454   | 1.59 (0.47-5.39)    |
|              |            |          |                  |               | TT 20 (1.8)       | 3 (1.1)              |         |                     |
| rs4424038    | 5          | q33.2    | 153740704        | GRIA1         | CC + CT 1102 (99.5)| 262 (100.0)          | 0.276   | ND                  |
|              |            |          |                  |               | TT 5 (0.5)        | 0 (0.0)              |         |                     |
| rs17035909   | 4          | q32.1    | 157247565        | GRIA2         | AA + AT 351 (31.7)| 87 (33.3)            | 0.640   | 1.07 (0.80-1.43)    |
|              |            |          |                  |               | TT 756 (68.3)     | 175 (66.7)           |         |                     |
| rs17035959   | 4          | q32.1    | 157302204        | GRIA2         | AA + AC 1075 (97.1)| 255 (97.3)           | 0.848   | 1.08 (0.47-2.48)    |
|              |            |          |                  |               | CC 32 (2.9)       | 7 (2.7)              |         |                     |
Table 1 Genotype distribution of glutamate receptor family gene SNPs in Taiwanese KD patients and controls (Continued)

| SNP         | Chromosome | Gene | Genotype | Patient Cases | Control Cases | Odds Ratio (95% CI) |
|-------------|------------|------|----------|---------------|---------------|-------------------|
| rs7695870   | 4          | GRIA2| CC + CT  | 1082 (97.7)   | 258 (98.5)    | 0.460 (0.51-4.32)  |
| rs6855973   | 4          | GRIA2| AA + AT  | 1085 (98)     | 258 (98.4)    | 0.623 (0.45-3.83)  |
| rs10895875  | 11         | GRIA4| AA + AT  | 715 (64.6)    | 181 (69.1)    | 0.169 (0.92-1.64)  |
| rs4754136   | 11         | GRIA4| CC + CT  | 1102 (99.5)   | 261 (99.6)    | 0.877 (0.14-1.10)  |
| rs17104835  | 11         | GRIA4| CC + CT  | 447 (40.4)    | 104 (39.8)    | 0.839 (0.74-1.28)  |
| rs7750018   | 6          | GRM1 | AA + AT  | 1085 (98)     | 258 (98.4)    | 0.623 (0.45-3.83)  |
| rs362851    | 6          | GRM1 | CC + CG  | 713 (64.4)    | 169 (64.5)    | 0.977 (0.76-1.33)  |
| rs2300631   | 6          | GRM1 | AA + AG  | 1076 (97.2)   | 253 (96.6)    | 0.583 (0.38-0.87)  |
| rs1983842   | 6          | GRM1 | AA + AG  | 1070 (96.7)   | 253 (96.6)    | 0.940 (0.46-2.04)  |
| rs802441    | 7          | GRM3 | AA + AG  | 1081 (97.6)   | 255 (97.3)    | 0.759 (0.38-2.04)  |
| rs802466    | 7          | GRM3 | AA + AG  | 1076 (98)     | 258 (98.5)    | 0.567 (0.38-0.82)  |
| rs12704286  | 7          | GRM3 | AA + AG  | 364 (32.9)    | 91 (34.8)     | 0.567 (0.82-1.44)  |
| rs17697415  | 7          | GRM3 | AA + AG  | 364 (32.9)    | 91 (34.8)     | 0.567 (0.82-1.44)  |
| rs1873254   | 6          | GRM4 | AA + AG  | 1090 (98.5)   | 260 (99.2)    | 0.337 (0.47-0.83)  |
| rs937039    | 6          | GRM4 | AA + AG  | 1090 (98.5)   | 260 (99.2)    | 0.337 (0.47-0.83)  |
| rs1565361   | 6          | GRM4 | CC + CT  | 503 (45.5)    | 117 (44.7)    | 0.819 (0.74-1.27)  |
| rs4106126   | 11         | GRM5 | CC + CT  | 1093 (98.7)   | 256 (97.7)    | 0.214 (0.21-1.44)  |
| rs1391878   | 11         | GRM5 | CC + CT  | 1093 (98.7)   | 256 (97.7)    | 0.214 (0.21-1.44)  |
| rs12787863  | 11         | GRM5 | AA + AG  | 447 (40.4)    | 110 (42.0)    | 0.634 (0.81-1.40)  |
| rs7126679   | 11         | GRM5 | AA + AG  | 651 (58.9)    | 160 (61.1)    | 0.513 (0.83-1.44)  |
| rs2856354   | 5          | GRM6 | AA + AG  | 1055 (95.3)   | 244 (93.1)    | 0.151 (0.38-1.16)  |
complications and the GRIK1 (rs466013, rs425507, rs38700 and rs402280) genetic variants were observed (Full model: for rs466013: odds ratio = 2.12; 95% CI = 1.22-3.65; for rs425507: odds ratio = 2.16; 95% CI = 1.26-3.76; for rs388700: odds ratio = 2.16; 95% CI = 1.26-3.76; for rs402280: odds ratio = 1.89; 95% CI = 1.09-3.21).

Taken together, these data suggest that the significant association observed between CAA complications and the presence of the GRIK1 genotypes persists even after adjusting for the potential factors.

**Discussion**

Previous research from our lab suggests that the NMDA receptor (GRIN3A) from the glutamate receptor family may influence KD pathogenesis [26]. In this study, we screened the entire glutamate receptor family including the iGluRs and mGluRs (GRIK, GRIA and GRM gene families) and identified another member, namely GRIK1, that may be involved in the development of KD-associated CAA complications in Taiwanese children of Han Chinese ethnic background. The most striking finding of this study is that 4 GRIK1 gene variants were found to be strongly associated with the presence of CAA in KD patients, even in the multivariable model.

Our genetic association study showed that none of the genes of the glutamate receptor gene family including GRIK1, GRIK2, GRIK3, GRIK4, GRIK5, GRIA1, GRIA2, GRIA4, GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, and GRM8 genes contributed to KD susceptibility. However, genetic variation of the GRIK1 locus may potential induce susceptibility to the development of KD with CAA complications. The significant association observed between KD with CAA complications and the GRIK1 genetic variants (rs466013, rs425507, rs38700, and rs402280) was found to persist even after adjusting for fever duration and first IVIG used time. These results suggest that the GRIK1 gene may be involved in CAA formation of KD. GRIK1 polymorphisms have been investigation for their associations with different diseases including Juvenile absence epilepsy [28,29], schizophrenia [30,31], alcohol dependence [32], topiramate’s effects on heavy drinking [33,34], topiramate-induced side effects [35], and hepatitis B virus (HBV)-related hepatocellular carcinoma [36]. However, these GRIK1 polymorphism data of various studies are also not absolutely consistent and conclusive. These studies show that GRIK1 gene may mainly contribute to neuropsychological diseases.

Glutamate is known to signal and is released by nerves,
Table 2: Association of the genetic variants of glutamate receptor family genes in Taiwanese KD children according to the presence or absence of CAA

| SNP  | Chromosome | Cytoband | Physical position | Nearest genes | KD CAA- No. (%) | KD CAA+ No. (%) | p value | Odds ratio (95% CI) |
|------|------------|----------|-------------------|---------------|----------------|----------------|---------|------------------|
| rs466013 | 21 | q21.3 | 29826390 | GRIK1 | TT + TC 83 (44.9) | 48 (63.2) | 0.007 | 2.11 (1.22 3.65) |
|       |            |          |                   |               | CC 102 (55.1) | 28 (36.8) |         |                  |
| rs425507 | 21 | q21.3 | 29827658 | GRIK1 | G + GA 82 (44.1) | 48 (63.2) | 0.01 | 2.17 (1.26 3.76) |
|       |            |          |                   |               | AA 104 (55.9) | 28 (36.8) |         |                  |
| rs388700 | 21 | q21.3 | 29830158 | GRIK1 | TT + TA 81 (44.1) | 48 (63.2) | 0.004 | 2.20 (1.27 3.81) |
|       |            |          |                   |               | AA 104 (55.9) | 28 (36.8) |         |                  |
| rs402280 | 21 | q21.3 | 29835401 | GRIK1 | TT + TA 74 (39.8) | 42 (55.2) | 0.022 | 1.87 (1.09 3.21) |
|       |            |          |                   |               | AA 112 (60.2) | 34 (44.8) |         |                  |
| rs17816480 | 6 | q16.3 | 101522140 | GRIK2 | TT + TC 30 (16.1) | 18 (23.7) | 0.151 | 1.61 (0.84 3.11) |
|       |            |          |                   |               | CC 156 (83.9) | 58 (76.3) |         |                  |
| rs2786239 | 6 | q16.3 | 101637565 | GRIK2 | GG + GA 29 (15.6) | 16 (21.1) | 0.288 | 1.44 (0.73 2.85) |
|       |            |          |                   |               | AA 157 (84.4) | 60 (76.9) |         |                  |
| rs4840194 | 6 | q16.3 | 101768497 | GRIK2 | CC + CT 64 (34.4) | 24 (31.6) | 0.660 | 0.88 (0.50 1.56) |
|       |            |          |                   |               | TT 122 (65.6) | 52 (68.4) |         |                  |
| rs1310715 | 6 | q16.3 | 101061427 | GRIK2 | TT + TC 91 (49.2) | 42 (55.3) | 0.373 | 1.28 (0.75 2.18) |
|       |            |          |                   |               | CC 94 (50.8) | 34 (44.7) |         |                  |
| rs527631 | 1 | p34.3 | 36844396 | GRIK3 | AA + AG 32 (17.6) | 13 (17.8) | 0.966 | 1.02 (0.50 2.07) |
|       |            |          |                   |               | GG 150 (82.4) | 60 (82.2) |         |                  |
| rs476894 | 1 | p34.3 | 36868682 | GRIK3 | GG + GA 45 (24.2) | 18 (23.7) | 0.930 | 0.97 (0.52 1.82) |
|       |            |          |                   |               | AA 141 (75.8) | 58 (76.3) |         |                  |
| rs541671 | 1 | p34.3 | 36905238 | GRIK3 | TT + TA 47 (26.1) | 18 (25.3) | 0.902 | 0.96 (0.51 1.80) |
|       |            |          |                   |               | AA 133 (73.9) | 53 (74.7) |         |                  |
| rs35317705 | 1 | p34.3 | 36972969 | GRIK3 | CC + CT 22 (11.8) | 11 (14.5) | 0.558 | 1.26 (0.58 2.75) |
|       |            |          |                   |               | TT 164 (88.2) | 65 (85.5) |         |                  |
| rs11218005 | 11 | q23.3 | 120782227 | GRIK4 | AA + AC 27 (14.5) | 8 (10.5) | 0.389 | 0.69 (0.30 1.60) |
|       |            |          |                   |               | CC 159 (85.5) | 68 (89.5) |         |                  |
| rs3901285 | 11 | q23.3 | 120862726 | GRIK4 | TT + TC 113 (60.7) | 45 (59.2) | 0.817 | 0.94 (0.54 1.62) |
|       |            |          |                   |               | CC 73 (39.3) | 31 (40.8) |         |                  |
| rs4936566 | 11 | q23.3 | 120944529 | GRIK4 | AA + AG 104 (55.9) | 41 (54.0) | 0.771 | 0.92 (0.54 1.58) |
|       |            |          |                   |               | GG 82 (44.1) | 35 (46.0) |         |                  |
| rs443239 | 19 | q13.2 | 42001892 | GRIK5 | CC + CG 45 (24.2) | 19 (25.0) | 0.890 | 1.04 (0.56 1.94) |
|       |            |          |                   |               | TT 164 (88.2) | 65 (85.5) |         |                  |
| rs1493395 | 5 | q33.2 | 153532297 | GRIA1 | AA + AG 88 (47.3) | 37 (48.7) | 0.840 | 1.06 (0.62 1.80) |
|       |            |          |                   |               | GG 98 (52.7) | 39 (51.3) |         |                  |
| rs12153489 | 5 | q33.2 | 153568777 | GRIA1 | TT + CT 40 (21.5) | 19 (25.0) | 0.539 | 1.22 (0.65 2.28) |
|       |            |          |                   |               | CC 146 (78.5) | 57 (75.0) |         |                  |
| rs4424038 | 5 | q33.2 | 153740704 | GRIA1 | TT + CT 23 (12.4) | 10 (13.2) | 0.861 | 1.07 (0.48 2.38) |
|       |            |          |                   |               | CC 163 (87.6) | 66 (86.8) |         |                  |
| rs17035909 | 4 | q32.1 | 157247565 | GRIA2 | AA + AT 66 (35.7) | 21 (27.6) | 0.210 | 0.69 (0.38 1.24) |
|       |            |          |                   |               | TT 119 (64.3) | 55 (72.4) |         |                  |
| rs17035959 | 4 | q32.1 | 157302204 | GRIA2 | CC + AC 72 (38.7) | 25 (32.9) | 0.376 | 0.78 (0.44 1.36) |
|       |            |          |                   |               | AA 114 (61.3) | 51 (67.1) |         |                  |
Table 2 Association of the genetic variants of glutamate receptor family genes in Taiwanese KD children according to the presence or absence of CAA

| Gene Symbol | Chromosome | Position | rsID | CR72 | G72 | OR (95% CI) |
|-------------|------------|----------|------|------|-----|-------------|
| rs7695870   | 4          | 157342624| GRIA2| TT + CT | 50 (26.9) | 26 (34.2) | 0.236 | 1.41  (0.80-2.51) |
| rs6855973   | 4          | 157365463| GRIA2| TT + AT | 60 (33.2) | 18 (24.0) | 0.148 | 0.64  (0.34-1.18) |
| rs10895875  | 11         | 105785485| GRIA4| AA + AT | 130 (69.9) | 51 (67.1) | 0.673 | 1.16  (0.58-2.30) |
| rs4754136   | 11         | 105846312| GRIA4| TT + CT | 56 (30.1) | 25 (32.9) | 0.092 | 0.43  (0.16-1.17) |
| rs17104835  | 11         | 105971356| GRIA4| CC + CT | 66 (35.7) | 38 (50)   | 0.032 | 1.80  (1.05-3.10) |
| rs7750018   | 6          | 146206595| GRM1 | TT + CT | 43 (23.1) | 19 (25.0) | 0.745 | 1.11  (0.60-2.06) |
| rs362851    | 6          | 146389448| GRM1 | CC + CG | 117 (62.9) | 52 (68.4) | 0.397 | 1.28  (0.72-2.25) |
| rs2300631   | 6          | 146428918| GRM1 | AA + AG | 135 (72.7) | 57 (75.0) | 0.688 | 1.13  (0.62-2.09) |
| rs12023603  | 1          | 51466999 | GRM2 | CC + CT | 56 (30.1) | 23 (30.2) | 0.980 | 1.01  (0.56-1.80) |
| rs1983842   | 1          | 51535259 | GRM2 | AA + CG | 136 (73.1) | 54 (71.1) | 1     |
| rs802441    | 7          | 86657787 | GRM3 | TT + CT | 51 (27.4) | 23 (30.2) | 0.643 | 1.15  (0.64-2.06) |
| rs802466    | 7          | 86698122 | GRM3 | CC + CT | 35 (18.8) | 9 (11.8)  | 0.171 | 0.58  (0.26-1.27) |
| rs12704286  | 7          | 86745625 | GRM3 | AA + AG | 60 (33.3) | 27 (38.6) | 0.435 | 1.26  (0.71-2.23) |
| rs17697415  | 7          | 86772500 | GRM3 | CC + CT | 35 (18.8) | 9 (11.8)  | 0.171 | 0.58  (0.26-1.27) |
| rs1873254   | 6          | 34058712 | GRM4 | AA + AG | 105 (57.4) | 43 (57.3) | 0.995 | 1.00  (0.58-1.72) |
| rs937039    | 6          | 34075875 | GRM4 | GG + AG | 78 (42.6) | 32 (42.7) | 0.823 | 0.93  (0.49-1.76) |
| rs1565361   | 6          | 34089248 | GRM4 | AA + CT | 84 (45.2) | 33 (43.4) | 0.797 | 0.93  (0.54-1.60) |
| rs4106126   | 11         | 88647181 | GRM5 | TT + CT | 43 (23.1) | 18 (23.7) | 0.922 | 1.03  (0.55-1.94) |
| rs1391878   | 11         | 88713212 | GRM5 | CC + CT | 39 (21.0) | 19 (25.0) | 0.476 | 1.26  (0.67-2.35) |
| rs12787863  | 11         | 88810547 | GRM5 | AA + AG | 77 (41.4) | 33 (43.4) | 0.763 | 1.09  (0.63-1.86) |
| rs7126679   | 11         | 89020677 | GRM5 | AA + AG | 109 (59.9) | 48 (64.0) | 0.539 | 1.19  (0.68-2.08) |
| rs2856354   | 5          | 178978728| GRM6 | GG + AG | 81 (43.6) | 37 (48.7) | 0.448 | 1.23  (0.72-2.10) |
Table 2 Association of the genetic variants of glutamate receptor family genes in Taiwanese KD children according to the presence or absence of CAA (Continued)

| SNP ID     | Chr | Physical Position | Gene | Genotype | N Cases with CAA | N Cases without CAA | p-value | OR (95% CI) |
|------------|-----|-------------------|------|----------|-----------------|---------------------|---------|-------------|
| rs10464073 | 5   | q35.3             | GRM6 | GG + AG  | 81 (43.6)       | 37 (48.7)           | 0.448   | 1.23 (0.72-2.10) |
|            |     |                   |      | AA       | 105 (56.4)      | 39 (51.3)           |         |             |
| rs17078880 | 5   | q35.3             | GRM6 | TT + CT  | 51 (27.7)       | 20 (26.7)           | 0.863   | 0.95 (0.52-1.74) |
|            |     |                   |      | CC       | 133 (72.3)      | 55 (73.3)           |         |             |
| rs2645341  | 5   | q35.3             | GRM6 | GG + AG  | 53 (28.5)       | 19 (25.0)           | 0.565   | 0.84 (0.45-1.54) |
|            |     |                   |      | AA       | 133 (71.5)      | 57 (75.0)           |         |             |
| rs6764411  | 3   | p26.1             | GRM7 | CC + AC  | 127 (68.3)      | 52 (68.4)           | 0.982   | 1.01 (0.57-1.79) |
|            |     |                   |      | AA       | 59 (31.7)       | 24 (31.6)           |         |             |
| rs17697928 | 3   | p26.1             | GRM7 | AA + AG  | 130 (69.9)      | 48 (63.2)           | 0.289   | 0.74 (0.42-1.29) |
|            |     |                   |      | GG       | 56 (30.1)       | 28 (36.8)           |         |             |
| rs779741   | 3   | p26.1             | GRM7 | CC + AC  | 124 (66.7)      | 48 (63.2)           | 0.587   | 0.86 (0.49-1.50) |
|            |     |                   |      | AA       | 62 (33.3)       | 28 (36.8)           |         |             |
| rs1354405  | 3   | p26.1             | GRM7 | GG + AG  | 103 (55.4)      | 38 (50.0)           | 0.428   | 0.81 (0.47-1.38) |
|            |     |                   |      | AA       | 83 (44.6)       | 38 (50.0)           |         |             |
| rs712723   | 7   | q31.33            | GRM8 | CC + CT  | 115 (61.8)      | 59 (77.6)           | 0.014   | 2.14 (1.16-3.6) |
| rs17627206 | 7   | q31.33            | GRM8 | TT + CT  | 71 (38.2)       | 20 (10.7)           | 0.957   | 0.98 (0.41-2.32) |
| rs11563505 | 7   | q31.33            | GRM8 | TT + CT  | 46 (24.7)       | 19 (25.0)           | 0.964   | 1.01 (0.55-1.88) |

Physical position of individual SNPs was based on the NCBI Assembly database: GRCh38 version.

GRIK, glutamate receptor, ionotropic, kainate; GRIA, glutamate receptor, ionotropic, AMPA; GRM, glutamate receptor, metabotropic; SNP, single nucleotide polymorphism; CI, confidence interval.
p-values were obtained by chi-square test (2 x 2 table).
Bold italic are significant at p value <0.05.

Figure 1 Analysis of single nucleotide polymorphisms (SNPs) and the linkage disequilibrium (LD) pattern of the GRIK1 gene. Genomic location of SNPs present on chromosome 21q21.3. Physical position of individual SNPs was based on the NCBI Assembly database: GRCh38 version. Linkage disequilibrium (LD) blocks in the GRIK1 gene, estimated by using HAPLOVIEW software. Pairwise D' values (%) are indicated in squares; red indicates linkage disequilibrium (D' =1, logarithm of odds (LOD) ≥2).
macrophages, lymphocytes, and chondrocytes [37,38]. These amino acids bind to iGluRs and mGluRs to regulate peripheral pain, release of cytokines and matrix metalloproteinases, and immune responses [39-41]. Our studies have firstly showed that glutamate receptors including NMDA [26] and KA receptors are involved in the CAA complications of KD regardless of the fever duration and first IVIG used time. KD is a multi-systemic disorder with a possible underlying pathology of immune-mediated vasculitis [1,42]. The vascular endothelium forms a functional barrier between the vessel wall and the bloodstream. Recent studies have shown that regulation of certain glutamate receptors may induce the inflammation of endothelial cells, thereby mediating pathogenesis of vascular diseases [43,44]. Although the current therapy for KD includes high doses of aspirin in conjunction with IVIG treatment [45], reports suggest that this regimen cannot efficiently prevent CAA development. In this study, we showed that the glutamate receptor GRIK1 is significantly associated with KD with CAA complications of Han Chinese individuals, who account for 98% of the Taiwanese residents, were considered for recruitment. This study was approved by the Human Studies Committee of China Medical University Hospital (CMUH REC No. DMR101-IRB1-313 (CR-1)).

Consent
The written informed consent was obtained from the patient's guardian/parent/next of kin for the publication of this report and any accompanying images.

SNP genotyping
Fifty-three single nucleotide polymorphisms (SNPs) of 16 genes within the glutamate receptor gene family including GRIK1, GRIK2, GRIK3, GRIK4, GRIK5, GRIA1, GRIA2, GRIA4, GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, and GRM8 were selected from the NCBI SNP database and HAPMAP website (Tables 2 and 3) [52]. Selection criteria for including SNPs in the analysis were a minimum allele frequency of >0.05 in the Han Chinese population and a Hardy-Weinberg equilibrium (p >0.05). A summary of information on the SNPs in the glutamate receptor genes (location, position, rs number, and genotype) is presented in Table 1. Briefly, genomic DNA was extracted from peripheral blood leukocytes according to the standard protocols (Genomic DNA kit; Qiagen). SNPs were genotyped using a custom-designed VeraCode GoldenGate Genotyping Assay System (Illumina); genotyping was performed as outlined in http://www.illumina.com/.

Primers and probes were designed and created using Custom VeraCode GoldenGate Genotyping Assay System software. Genotype calls were automatically generated using GenCall software version 3.1.3. We assessed the 8 VeraCode runs individually for intra-plate inconsistencies (e.g., variation in fluorescence intensities). Genotype cluster plots generated by individual VeraCode and SAM assays were visually inspected for call quality. Plots that appeared to be “unusually” clustered (i.e., unlike the predicted spread in terms of software-generated HWE or

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Table 3 Association of GRIK1 genetic polymorphisms with CAA complications in Taiwanese KD children by multivariate regression analysis

| GRIK1 genetic polymorphisms | Odds ratio | 95% CI | p value |
|-----------------------------|------------|--------|---------|
| Full model (adjusted by fever duration and first IVIG used time) | | | |
| rs466013                    | 2.12       | 1.22-3.65 | 0.011  |
| rs425507                    | 2.16       | 1.26-3.76 | 0.009  |
| rs388700                    | 2.16       | 1.26-3.76 | 0.009  |
| rs402280                    | 1.89       | 1.09-3.21 | 0.028  |

GRIK1, glutamate receptor, ionotropic, kainate 1; IVIG, Intravenous immunoglobulin; CAA, Coronary artery aneurysm; CI, confidence interval. Full model shows results from a logistic regression model including the indicated predictors, fever duration (days) and first IVIG used time (number of days after the first day of fever). Bold italic are significant at p value <0.05.
distance between clusters [9] were investigated further by selecting samples via direct Sanger sequencing for genotype confirmation. Samples were sequenced using Big Dye Terminator v3.1 (AB, Foster City, CA, USA) according to the manufacturer's guidelines, and sequenced with an AB 3730 genetic analyzer.

Analysis of haplotype blocks

Based on the HAPLOVIEW software, we used the Lewontin D' measure to estimate the intermarker coefficient of LD of patients [53]. The confidence interval (CI) of LD was estimated using a resampling procedure and then used to construct the haplotype blocks.

Statistical analyses

Data are expressed as means ± standard deviation for continuous variables. Genotypes were obtained by direct sequencing selecting samples via direct Sanger sequencing for geno-

Additional files

Data are expressed as means ± standard deviation for continuous variables. Genotypes were obtained by direct sequencing selecting samples via direct Sanger sequencing for geno-

### Additional file 1: Figure S1.

Search results of single nucleotide polymorphisms (SNPs) of rs466013 from 4 GWAS studies were used for searching for common gene SNPs by using Venny website (http://bioinfogp.cnb.csic.es/tools/venny/).

Figure S2.

Figure S3.

Figure S4.

Figure S5.

Genetic variations within the PSORS1 region affect Kawasaki disease development and coronary artery aneurysm formation. Biomed 2013, 3:73–81.

Chang CI, Kuo HC, Chang JS, Lee JK, Tsai FJ, Khor CC, Chang LC, Chen SP, Kim JJ, Park YM, Yoon D, Lee KY, Seob Song M, Doo Lee H, Kim KJ, Park IS, Yan Y, Ma Y, Liu Y, Hu H, Shen Y, Zhang S, Tao D, Wu Q, Peng Q, Yang Y.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

YJL, JSC, XL, and FJT conceived and designed the experiments. THL, CCL, SMH, CWL, and HT performed the experiments. WKC and JHC analyzed the data. JSC, XL, JYW, CHC, LCC, and TJH contributed reagents/materials/analysis tools. YJL and XL wrote the manuscript. All the authors have read and approved the final manuscript.

Acknowledgments

The authors wish to thank the Department of Pediatrics, China Medical University Hospital (CMUH) for administrative assistance and China Medical University (CMU) under the Aim for Top University Plan of the Ministry of Education, Taiwan. We also thank Drs. Kuan-Teh Jeang, Chia-Yen Chen, and Willy W. L. Hong for technical help and suggestions.

Funding

Financial support for this research was provided by CMU (CMU100-S-01), CMUH (DMD-103-039), and the Republic of China National Science Council (NSC100-2320-B-039-012-MY3).

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Received: 7 February 2014 Accepted: 20 October 2014 Published: 19 November 2014

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### Additional file 2: Table S1.

Characteristics of GWAS studies for KD susceptibility included in this meta-analysis. Table S2. Meta-analysis for previous reported GWAS studies for KD susceptibility.
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doi:10.1186/2045-3701-4-67

Cite this article as: Lin et al: Genetic variants of glutamate receptor gene family in Taiwanese Kawasaki disease children with coronary artery aneurysms. Cell & Bioscience 2014 4:67.

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