

## Supplementary materials

# Toxicity and Metabolomic Dysfunction Invoked by Febrifugin, a Harmful Component of Edible Nut of *Swietenia macrophylla*

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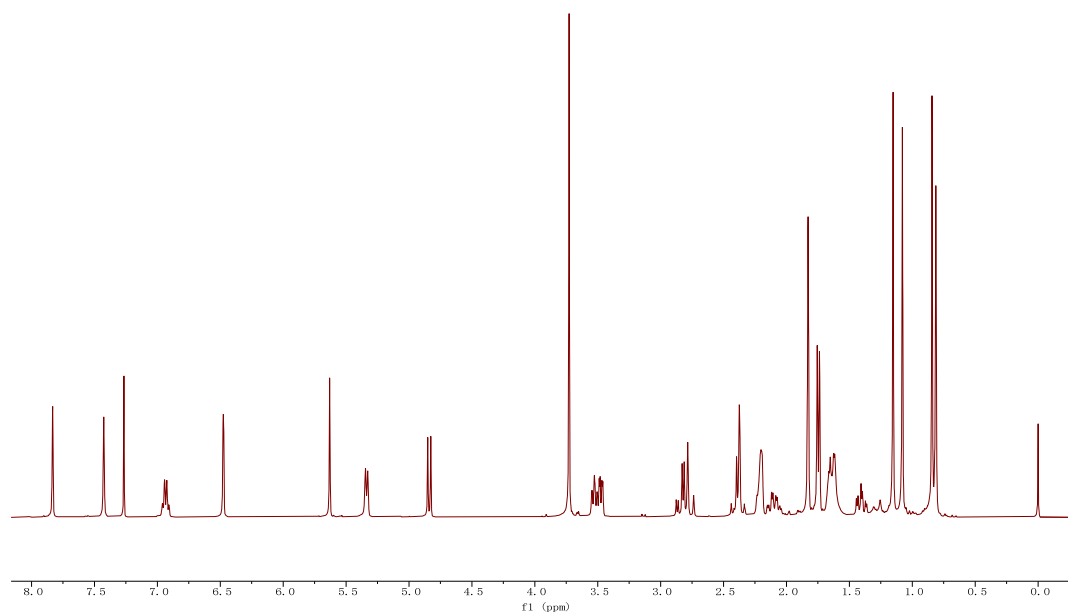
Figure S1. <sup>1</sup>H (400 MHz), <sup>13</sup>C (100 MHz) NMR and LC-MS/MS spectrum of Febrifugin.

Table S1. Metabolic enrichment results based on Fella ( $p < 0.01$ )

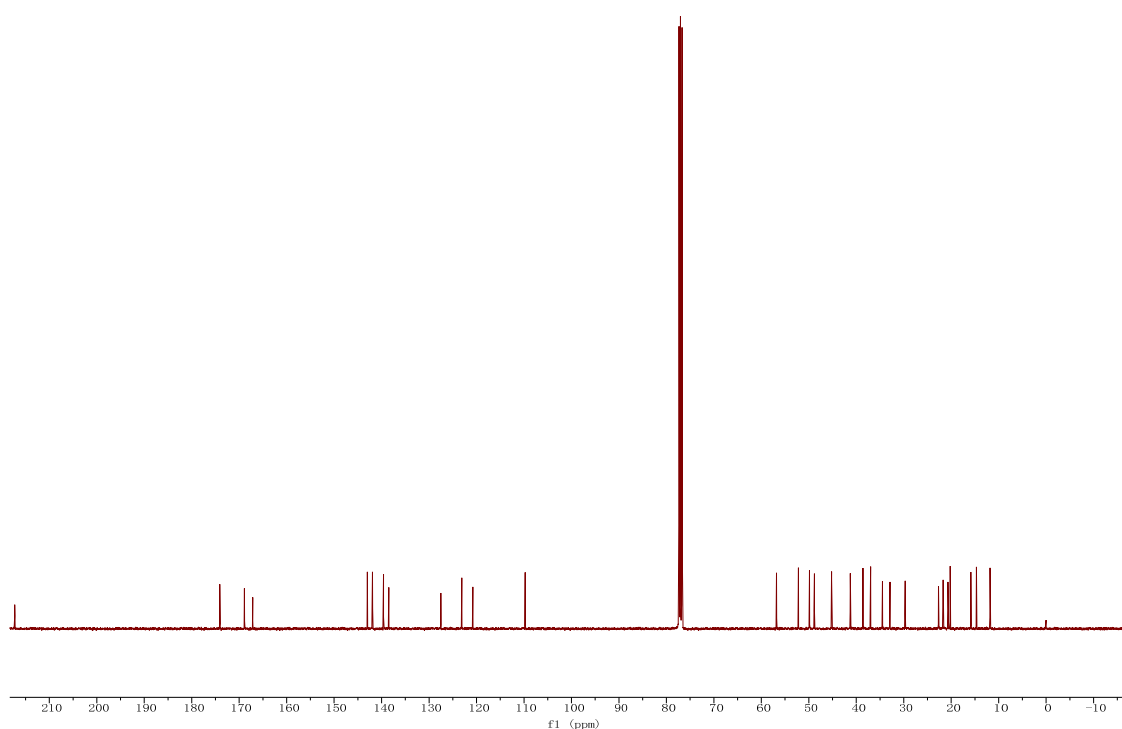
Table S2. Primers used for qPCR analysis

Table S3. qPCR analysis results.

**Figure S1.**  $^1\text{H}$  (400 MHz),  $^{13}\text{C}$  (100 MHz) NMR and LC-MS/MS spectrum of Febrifugin.

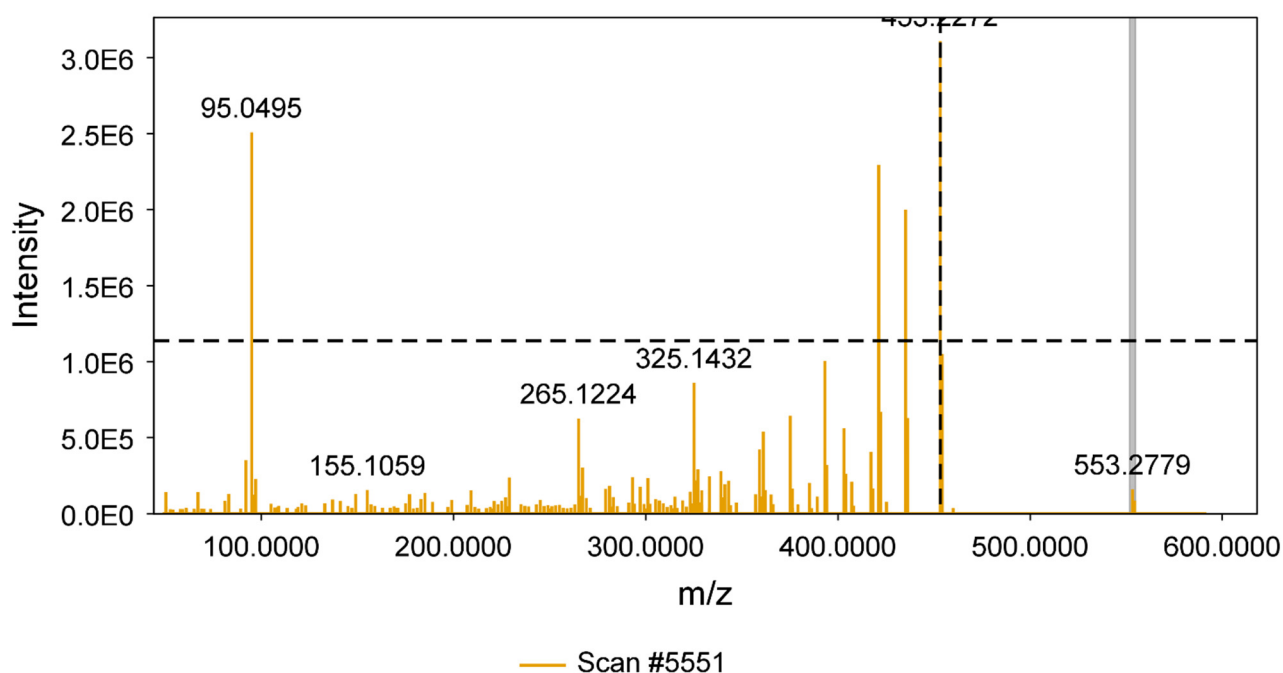


$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.80-0.90(m,2H),1.05-1.5(m,3H),1.53-1.82(m,4H),2.10-2.40(m,4H),2.75-2.82(m,3H),3.48-3.75(m,3H),4.85(d,1H),5.35(m,1H),5.65(s,1H),6.47(s,1H),6.95(m,1H),7.42-7.83(m,2H).



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  217.30, 174.08, 168.89, 167.14, 143.00, 141.91, 139.60, 138.49, 127.53, 123.10, 120.79,

109.74, 77.35, 77.08, 77.03, 76.71, 76.64, 56.80, 52.19, 49.85, 48.82, 45.19, 41.26, 38.61, 36.98, 34.49, 32.91, 29.69, 22.66, 21.70, 20.67, 20.22, 15.85, 14.68, 11.82, 0.00.



Found m/z 553.2779

**Table S1. Metabolic enrichment results based on Fella ( $p < 0.01$ )**

| KEGG.id  | Entry.type | KEGG.name  | p.score  |
|----------|------------|--|----------|
| dre00030 | pathway    | Pentose phosphate pathway - Danio rerio (zebr... | 0.000123 |
| dre00020 | pathway    | Citrate cycle (TCA cycle) - Danio rerio (zebr... | 0.000140 |
| dre00250 | pathway    | Alanine, aspartate and glutamate metabolism -... | 0.007235 |
| dre01200 | pathway    | Carbon metabolism - Danio rerio (zebrafish)      | 0.012266 |
| M00004   | module     | Pentose phosphate pathway (Pentose phosphate ... | 0.000001 |
| M00006   | module     | Pentose phosphate pathway, oxidative phase, g... | 0.000001 |
| M00008   | module     | Entner-Doudoroff pathway, glucose-6P => glyce... | 0.000001 |
| M00051   | module     | De novo pyrimidine biosynthesis, glutamine (+... | 0.000001 |
| M00010   | module     | Citrate cycle, first carbon oxidation, oxaloa... | 0.000002 |
| M00173   | module     | Reductive citrate cycle (Arnon-Buchanan cycle... | 0.000003 |
| M00012   | module     | Glyoxylate cycle                                 | 0.000118 |
| M00368   | module     | Ethylene biosynthesis, methionine => ethylene    | 0.000403 |

|            |        |   |          |
|------------|--------|---|----------|
| M00009     | module | Citrate cycle (TCA cycle, Krebs cycle)                        | 0.000451 |
| M00133     | module | Polyamine biosynthesis, arginine => agmatine ...              | 0.000985 |
| M00005     | module | PRPP biosynthesis, ribose 5P => PRPP                          | 0.001915 |
| M00171     | module | C4-dicarboxylic acid cycle, NAD - malic enzym...              | 0.009360 |
| 1.1.1.343  | enzyme | phosphogluconate dehydrogenase (NAD <sup>+</sup> -dependen... | 0.000001 |
| 1.1.1.44   | enzyme | phosphogluconate dehydrogenase (NADP <sup>+</sup> -depende... | 0.000001 |
| 1.3.1.24   | enzyme | biliverdin reductase  | 0.000001 |
| 1.3.5.2    | enzyme | dihydroorotate dehydrogenase (quinone)                        | 0.000001 |
| 2.3.3.1    | enzyme | citrate (Si)-synthase   | 0.000001 |
| 2.3.3.8    | enzyme | ATP citrate synthase  | 0.000001 |
| 2.4.2.10   | enzyme | orotate phosphoribosyltransferase                             | 0.000001 |
| 3.1.1.31   | enzyme | 6-phosphogluconolactonase                                     | 0.000001 |
| 3.5.2.3    | enzyme | dihydroorotase  | 0.000001 |
| 4.2.1.3    | enzyme | aconitate hydratase   | 0.000001 |
| 4.6.1.15   | enzyme | FAD-AMP lyase (cyclizing)                                     | 0.000001 |
| 6.3.5.5    | enzyme | carbamoyl-phosphate synthase (glutamine-hydro...              | 0.000001 |
| 2.5.1.16   | enzyme | spermidine synthase   | 0.000001 |
| 1.14.14.18 | enzyme | heme oxygenase (biliverdin-producing)                         | 0.000001 |
| 2.6.1.42   | enzyme | branched-chain-amino-acid transaminase                        | 0.000003 |
| 2.5.1.22   | enzyme | spermine synthase   | 0.000004 |
| 2.1.3.2    | enzyme | aspartate carbamoyltransferase                                | 0.000005 |
| 2.4.2.28   | enzyme | S-methyl-5'-thioadenosine phosphorylase                       | 0.000008 |
| 2.6.1.5    | enzyme | tyrosine transaminase   | 0.000008 |
| 4.1.1.23   | enzyme | orotidine-5'-phosphate decarboxylase                          | 0.000133 |
| 1.1.1.49   | enzyme | glucose-6-phosphate dehydrogenase (NADP <sup>+</sup> )        | 0.000213 |
| 6.4.1.1    | enzyme | dan'shing'f   | 0.000343 |
| 1.1.1.41   | enzyme | isocitrate dehydrogenase (NAD <sup>+</sup> )                  | 0.000977 |
| 1.13.11.27 | enzyme | 4-hydroxyphenylpyruvate dioxygenase                           | 0.002373 |
| 1.1.1.363  | enzyme | glucose-6-phosphate dehydrogenase [NAD(P) <sup>+</sup> ]      | 0.002633 |
| 1.3.8.7    | enzyme | medium-chain acyl-CoA dehydrogenase                           | 0.002668 |

|          |          |  |          |
|----------|----------|--|----------|
| 4.1.1.50 | enzyme   | adenosylmethionine decarboxylase       | 0.003894 |
| 1.1.1.47 | enzyme   | glucose 1-dehydrogenase [NAD(P)+]      | 0.004008 |
| 1.3.8.8  | enzyme   | long-chain acyl-CoA dehydrogenase      | 0.004734 |
| 4.2.1.2  | enzyme   | fumarate hydratase                     | 0.005061 |
| 6.3.1.17 | enzyme   | beta-citrylglutamate synthase          | 0.005553 |
| 1.3.8.9  | enzyme   | very-long-chain acyl-CoA dehydrogenase | 0.005802 |
| 2.7.7.2  | enzyme   | FAD synthase                           | 0.008679 |
| 1.3.3.6  | enzyme   | acyl-CoA oxidase                       | 0.008960 |
| 1.3.5.1  | enzyme   | succinate dehydrogenase                | 0.009660 |
| C00016   | compound | FAD                                    | 0.000001 |
| C00108   | compound | Anthranilate                           | 0.000001 |
| C00158   | compound | Citrate                                | 0.000001 |
| C00170   | compound | 5'-Methylthioadenosine                 | 0.000001 |
| C00233   | compound | 4-Methyl-2-oxopentanoate               | 0.000001 |
| C00295   | compound | Orotate                                | 0.000001 |
| C00345   | compound | 6-Phospho-D-gluconate                  | 0.000001 |
| C00500   | compound | Biliverdin                             | 0.000001 |
| C01179   | compound | 3-(4-Hydroxyphenyl)pyruvate            | 0.000001 |
| C01494   | compound | Ferulate                               | 0.000001 |
| C00337   | compound | (S)-Dihydroorotate                     | 0.000012 |
| C01352   | compound | FADH2                                  | 0.000256 |

**Table S2. Primers used for qPCR analysis**

| Gene Symbol | Oligo Name | Sequence (5' to 3')      |
|-------------|------------|--------------------------|
| <i>pgd</i>  | pgd-F      | CAAGGACGCAGACGGCACTAAC   |
|             | pgd-R      | GACGAGAGGCATCTGGCAAAGAC  |
| <i>pgls</i> | pgls-F     | GCCGAGGACTATGCCAGCAAAC   |
|             | pgls-R     | TCCCATTTCCAGCAACAAGACATC |
| <i>h6pd</i> | h6pd-F     | CACGGCAACCTCCAATACCCTTC  |
|             | h6pd-R     | CTTCCAGTCACCGCTGCTCAC    |
| <i>cs</i>   | cs-F       | CGTGAAGGCAGCAGCATCGG     |
|             | cs-R       | CTGTGAACTGTGGCTCGGTGTATC |

|                |           |                           |
|----------------|-----------|---------------------------|
| <i>bcat1</i>   | bcat1-F   | AGAACTTGCTCGCCAATGGAGTG   |
|                | bcat1-R   | CTGCCGACTGGACTGACAACAC    |
| <i>cad</i>     | cad -F    | GACGATGCTGCCTCTGCTGTTC    |
|                | cad -R    | CTCCTGCTCCAAATCCACCTCAAC  |
| <i>lacc1</i>   | lacc1-F   | TGATGTGTGGGTGATGGGCAAAC   |
|                | lacc1-R   | CAGGGTCAGTGAAGAGCAATGGC   |
| <i>mtap</i>    | mtap-F    | GGAGGGAAGGACAGAGCGGTATG   |
|                | mtap-R    | TTGGCATGATGGTGTGTTGTCTCC  |
| <i>tat</i>     | tat-F     | CAGCGTGTTGTGTAACCCAGGAG   |
|                | tat-R     | CAGGACTTCTCAGGCAGCAGATTG  |
| <i>aclya</i>   | aclya-F   | GCTCTGGATGCCGCTGCTAAG     |
|                | aclya-R   | CCTGTGCCCCGATGCCCATATG    |
| <i>acol</i>    | acol-F    | GCCCTAAACGACCACATGACAGAG  |
|                | acol-R    | AACTGGAACGGCACTTGGACATC   |
| <i>g6pd</i>    | g6pd-F    | TGTAAAGAACGAACGCTGGGATGG  |
|                | g6pd-R    | GCAGACGCACCTCCGCTTTC      |
| <i>pcxa</i>    | pcxa-F    | CTTCACATCAAGGCTCTGGCTCTG  |
|                | pcxa-R    | TTCAGGGCTTTAGGGTGGAAATGC  |
| <i>idh3a</i>   | idh3a-F   | GGATTGATTGGCGGTCTTGGAGTC  |
|                | idh3a-R   | TCATGACGGCACTAAGCAAAAGGG  |
| <i>fh</i>      | fh-F      | CGGAGGAGTCACGGAGAGGATG    |
|                | fh-R      | ATGATGGCGTCTGCGATCTTTGG   |
| <i>sdha</i>    | sdha-F    | GTGCCTGTGCCCTGACCATTG     |
|                | sdha-R    | TTAGCGACCGATGCCTCTCCTG    |
| <i>β-actin</i> | β-actin-F | AACGAACGACCAACCTAAACCTCTC |
|                | β-actin-R | CTCCCTTTCCAGTTTCCGCATCC   |

**Table S3. qPCR analysis results.**

| gene symbol  | Group | Fold change |
|--------------|-------|-------------|
| <i>aclya</i> | G0    | 1.424667252 |
| <i>aclya</i> | G0    | 1.210518393 |
| <i>aclya</i> | G0    | 1.480028544 |
| <i>aclya</i> | G1    | 2.181015465 |
| <i>aclya</i> | G1    | 1.399585866 |
| <i>aclya</i> | G1    | 1.060687741 |
| <i>aclya</i> | G2    | 1.602139755 |

|              |    |             |
|--------------|----|-------------|
| <i>aclya</i> | G2 | 2.281527432 |
| <i>aclya</i> | G2 | 2.117702602 |
| <i>acol</i>  | G0 | 0.974764084 |
| <i>acol</i>  | G0 | 0.624435732 |
| <i>acol</i>  | G0 | 0.610526152 |
| <i>acol</i>  | G1 | 1.326385371 |
| <i>acol</i>  | G1 | 1.57734692  |
| <i>acol</i>  | G1 | 0.78867346  |
| <i>acol</i>  | G2 | 0.891928519 |
| <i>acol</i>  | G2 | 0.896577376 |
| <i>acol</i>  | G2 | 1.012203943 |
| <i>bcatl</i> | G0 | 1.79082579  |
| <i>bcatl</i> | G0 | 0.854483773 |
| <i>bcatl</i> | G0 | 1.708967546 |
| <i>bcatl</i> | G1 | 2.882858447 |
| <i>bcatl</i> | G1 | 3.60500185  |
| <i>bcatl</i> | G1 | 1.783857039 |
| <i>bcatl</i> | G2 | 2.620786808 |
| <i>bcatl</i> | G2 | 2.808889751 |
| <i>bcatl</i> | G2 | 2.979354926 |
| <i>cad</i>   | G0 | 2.497742928 |
| <i>cad</i>   | G0 | 0.935056211 |
| <i>cad</i>   | G0 | 2.208589046 |
| <i>cad</i>   | G1 | 3.910898245 |
| <i>cad</i>   | G1 | 2.775023521 |
| <i>cad</i>   | G1 | 1.474269217 |
| <i>cad</i>   | G2 | 1.670175839 |
| <i>cad</i>   | G2 | 2.449521577 |
| <i>cad</i>   | G2 | 5.511710068 |
| <i>cs</i>    | G0 | 0.988371284 |

|             |    |             |
|-------------|----|-------------|
| <i>cs</i>   | G0 | 0.595892915 |
| <i>cs</i>   | G0 | 0.689262294 |
| <i>cs</i>   | G1 | 1.431472545 |
| <i>cs</i>   | G1 | 1.602139755 |
| <i>cs</i>   | G1 | 1.128964405 |
| <i>cs</i>   | G2 | 0.840896415 |
| <i>cs</i>   | G2 | 0.981118975 |
| <i>cs</i>   | G2 | 0.656333056 |
| <i>fh</i>   | G0 | 0.951400705 |
| <i>fh</i>   | G0 | 0.767439539 |
| <i>fh</i>   | G0 | 0.925384603 |
| <i>fh</i>   | G1 | 1.610490332 |
| <i>fh</i>   | G1 | 1.869302432 |
| <i>fh</i>   | G1 | 1.385109468 |
| <i>fh</i>   | G2 | 1.084853325 |
| <i>fh</i>   | G2 | 1.513092304 |
| <i>fh</i>   | G2 | 1.189207115 |
| <i>g6pd</i> | G0 | 0.917798911 |
| <i>g6pd</i> | G0 | 0.701614272 |
| <i>g6pd</i> | G0 | 0.78935709  |
| <i>g6pd</i> | G1 | 1.141258021 |
| <i>g6pd</i> | G1 | 0.815425512 |
| <i>g6pd</i> | G1 | 0.740014272 |
| <i>g6pd</i> | G2 | 0.973076409 |
| <i>g6pd</i> | G2 | 0.958018221 |
| <i>g6pd</i> | G2 | 1.457125359 |
| <i>h6pd</i> | G0 | 0.992232419 |
| <i>h6pd</i> | G0 | 0.721339334 |
| <i>h6pd</i> | G0 | 0.638938952 |
| <i>h6pd</i> | G1 | 1.313234904 |



|              |    |             |
|--------------|----|-------------|
| <i>h6pd</i>  | G1 | 1.636512929 |
| <i>h6pd</i>  | G1 | 1.147206418 |
| <i>h6pd</i>  | G2 | 0.635350676 |
| <i>h6pd</i>  | G2 | 0.954703729 |
| <i>h6pd</i>  | G2 | 0.712333626 |
| <i>idh3a</i> | G0 | 0.918594468 |
| <i>idh3a</i> | G0 | 0.771105413 |
| <i>idh3a</i> | G0 | 0.809442217 |
| <i>idh3a</i> | G1 | 1.512436949 |
| <i>idh3a</i> | G1 | 1.874979731 |
| <i>idh3a</i> | G1 | 1.132393207 |
| <i>idh3a</i> | G2 | 1.078760798 |
| <i>idh3a</i> | G2 | 1.391725803 |
| <i>idh3a</i> | G2 | 1.618183257 |
| <i>lacc1</i> | G0 | 1.79082579  |
| <i>lacc1</i> | G0 | 0.854483773 |
| <i>lacc1</i> | G0 | 1.708967546 |
| <i>lacc1</i> | G1 | 2.882858447 |
| <i>lacc1</i> | G1 | 3.60500185  |
| <i>lacc1</i> | G1 | 1.783857039 |
| <i>lacc1</i> | G2 | 2.620786808 |
| <i>lacc1</i> | G2 | 2.808889751 |
| <i>lacc1</i> | G2 | 2.979354926 |
| <i>mtap</i>  | G0 | 2.497742928 |
| <i>mtap</i>  | G0 | 0.935056211 |
| <i>mtap</i>  | G0 | 2.208589046 |
| <i>mtap</i>  | G1 | 3.910898245 |
| <i>mtap</i>  | G1 | 2.775023521 |
| <i>mtap</i>  | G1 | 1.474269217 |
| <i>mtap</i>  | G2 | 1.670175839 |

|             |    |             |
|-------------|----|-------------|
| <i>mtap</i> | G2 | 2.449521577 |
| <i>mtap</i> | G2 | 5.511710068 |
| <i>pcxa</i> | G0 | 1           |
| <i>pcxa</i> | G0 | 0.86154616  |
| <i>pcxa</i> | G0 | 0.806641759 |
| <i>pcxa</i> | G1 | 1.623801182 |
| <i>pcxa</i> | G1 | 1.830039769 |
| <i>pcxa</i> | G1 | 1.124571196 |
| <i>pcxa</i> | G2 | 1.060228333 |
| <i>pcxa</i> | G2 | 1.544216464 |
| <i>pcxa</i> | G2 | 1.749417948 |
| <i>pgd</i>  | G0 | 1.325236643 |
| <i>pgd</i>  | G0 | 0.563016848 |
| <i>pgd</i>  | G0 | 0.623624711 |
| <i>pgd</i>  | G1 | 1.378524588 |
| <i>pgd</i>  | G1 | 1.553610655 |
| <i>pgd</i>  | G1 | 1.17945878  |
| <i>pgd</i>  | G2 | 0.656617452 |
| <i>pgd</i>  | G2 | 1.059310113 |
| <i>pgd</i>  | G2 | 1.100473954 |
| <i>pgls</i> | G0 | 1.040210135 |
| <i>pgls</i> | G0 | 0.615305588 |
| <i>pgls</i> | G0 | 0.741940295 |
| <i>pgls</i> | G1 | 1.013081331 |
| <i>pgls</i> | G1 | 1.23648951  |
| <i>pgls</i> | G1 | 0.976877794 |
| <i>pgls</i> | G2 | 0.582871594 |
| <i>pgls</i> | G2 | 0.543838427 |
| <i>pgls</i> | G2 | 0.892701651 |
| <i>sdha</i> | G0 | 0.945647887 |

|             |    |             |
|-------------|----|-------------|
| <i>sdha</i> | G0 | 0.758843875 |
| <i>sdha</i> | G0 | 0.927793086 |
| <i>sdha</i> | G1 | 1.374350518 |
| <i>sdha</i> | G1 | 1.757774496 |
| <i>sdha</i> | G1 | 1.221581399 |
| <i>sdha</i> | G2 | 1.10860852  |
| <i>sdha</i> | G2 | 1.242934266 |
| <i>sdha</i> | G2 | 0.978572062 |
| <i>tat</i>  | G0 | 1.575298251 |
| <i>tat</i>  | G0 | 1.145220182 |
| <i>tat</i>  | G0 | 1.688362861 |
| <i>tat</i>  | G1 | 2.7463205   |
| <i>tat</i>  | G1 | 2.67585511  |
| <i>tat</i>  | G1 | 1.385109468 |
| <i>tat</i>  | G2 | 1.796264746 |
| <i>tat</i>  | G2 | 2.432601496 |
| <i>tat</i>  | G2 | 2.634446716 |

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