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Reply to Comments on ‘A functional polymorphism rs10830963 in melatonin receptor 1B associated with the risk of gestational diabetes mellitus’

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To the editor,

Many thanks to Professor Klara Rosta, M.D., Ph.D., Gábor Firneisz, M.D., Ph.D., et al. for their interest on our recently published article, ‘A functional polymorphism rs10830963 in melatonin receptor 1B associated with the risk of gestational diabetes mellitus’ [1] and appreciate their comments [2] on it. We believe that peer exchanges among different research groups can promote better research works.

In the recent study, according to 14 reported research data on the association between a functional polymorphism rs10830963 in MTNR1B gene and the risk of gestational diabetes mellitus, we performed a meta-analysis by using Stata software, version 12.0 (Stata Corp LP, College Station, TX, U.S.A.) [3,4]. The false positive report probability (FPRP) analyses were adopted to confirm the positive findings [5,6]. Klara Rosta, M.D., Ph.D., et al. paid attention to one included study (good works from Rosta et al., 2017) in this meta-analysis, then put forward some opinions and suggestions on the minor (rs10830963 G) allele frequencies (MAF), the calculation of effect value (odds ratios, ORs) and the indication of relevant clinical data (mean age and pre-pregnancy BMI). We are here to respond. If there are any inaccuracies in our response, we welcome to communicate again.

Since we read the original literature of Rosta et al., 2017 [7], we found that not the exact genotyping data but an MAF of each studied SNP locus, including rs10830963 was reported. Therefore, we can not extract the accurate sample size data of being successfully genotyped. According to the number of 287 GDM cases meet the International Association of the Diabetes and Pregnancy Study Group (IADPSG) criteria and 533 controls reported in the literature, we estimated the genotype data by using the Hardy–Weinberg equilibrium (HWE) genotype distributions. The approach is recognized. As reminded by the commentary, we have carefully verified the extraction MAF in the literature, and hereby we correct it and other relevant research data.

We recalculate the results using the new genotype data, and the association between the SNP rs10830963 and the risk of GDM is still confirmed (Figures 1–3). Further functional experimental studies are warranted to explore and clarify the potential mechanism. Meanwhile, the variant rs10830963 G allele was estimated significantly associated with an increased GDM risk (CG vs. CC: OR = 1.44, 95% CI = 1.06–1.95; GG vs. CC: OR = 2.06, 95% CI = 1.26–3.37; G vs. C: OR = 1.44, 95% CI = 1.16–1.78) in the meta-analysis for Rosta et al.’s study data (Figures 1–3). There are slightly different of OR and corresponding 95% CI from the original literature. Maybe it was caused by meta-analysis process for different algorithms with stata software.
### Table 1 Characteristics of the studies included in the meta-analysis

| Author, year | Country | Diagnostic criteria | Genotyping methods | Controls | Number of case/control | MAF case/control | Mean age of cases/controls | Mean BMI of cases/controls | $P_{\text{HWE}}$ for controls | NOS score |
|--------------|---------|---------------------|--------------------|----------|------------------------|-----------------|---------------------------|----------------------------|-----------------------------|-----------|
| Deng Z., 2011 | China   | ADA                 | Sequencing         | NGT      | 87/91                  | 0.52/0.41       | 31.8 ± 4.6/29.7 ± 3.5    | 23.6 ± 3.0/21.5 ± 2.4     | 0.84                        | 4         |
| Kim J.Y., 2011 | Korea   | ADA                 | TaqMan             | NGT      | 906/966                | 0.52/0.45       | 33.1/32.2                | 23.3 ± 4.0/21.4 ± 2.9     | 0.53                        | 7         |
| Wang Y., 2011  | China   | ADA                 | TaqMan             | NGT      | 700/1029               | 0.46/0.43       | 30.0/32.0                | 21.5/21.7                  | 0.81                        | 8         |
| Vlassi M., 2012 | Greece  | ADA                 | PCR-RFLP           | NGT      | 77/98                  | 0.41/0.28       | 35.4 ± 4.4/31.3 ± 5.2    | 25.8 ± 5.1/26.7 ± 6.2     | 0.02                        | 4         |
| Huopio H., 2013 | Finland | ADA                 | Sequenom/Assay/TaqMan | NGT | 533/407                | 0.47/0.35       | 32.6/29.9                | 26.3 ± 4.7/24.1 ± 3.8     | 0.98                        | 8         |
| Li C., 2013    | China   | IADPSG              | PCR-RFLP           | NGT      | 350/480                | 0.45/0.40       | 32.4 ± 4.6/31.9 ± 5.2    | 25.3 ± 5.2/24.6 ± 4.6     | 0.79                        | 8         |
| Qi J., 2013    | China   | IADPSG              | Sequencing         | NGT      | 110/110                | 0.54/0.44       | 28.7 ± 3.1/28.1 ± 2.4    | NA/NA                      | 0.43                        | 6         |
| Vejradkova O., 2014 | Czech | WHO                | TaqMan             | NGT      | 458/422                | 0.36/0.29       | 34.1 ± 6.1/34.8 ± 15.1   | 24.3 ± 4.9/23.7 ± 4.2     | 0.48                        | 8         |
| Wang X., 2014  | China   | ADA                 | PCR-RFLP           | NGT      | 184/235                | 0.42/0.45       | 28.2 ± 3.8/27.9 ± 4.1    | 21.2 ± 1.8/20.7 ± 1.4     | 0.53                        | 6         |
| Junior J.P., 2015 | Brazil | ADA     | real-time PCR      | Healthy pregnant | 183/183               | 0.28/0.20        | 32/29                    | 32.0/25.4                  | 0.11                        | 7         |
| Liu Q., 2015   | China   | ADA                 | TaqMan             | NGT      | 674/674                | 0.51/0.44       | 31.6/32.1                | 24.4/25.2                  | 0.02                        | 8         |
| Tarnowski M., 2017 | Poland | IADPSG             | TaqMan             | NGT      | 204/207                | 0.39/0.31       | 31.7 ± 4.5/29.2 ± 5.0    | 25.1 ± 5.5/23.0 ± 4.0     | 0.112                       | 7         |
| Popova P.V., 2017 | Russia | ADA                | RT-PCR             | Healthy pregnant | 278/179               | 0.35/0.31       | 31.8 ± 4.8/29.4 ± 4.8    | 25.7 ± 5.9/22.9 ± 4.5     | 0.426                       | 6         |
| Rosta K., 2017 | Hungary and Austria | IADPSG             | KASP assay         | Healthy pregnant | 287/533               | 0.36/0.28       | Hungary:33.70/31.25; Austria:32.04/30.51 | Hungary:26.78/23.32; Austria:28.31/23.40 | 0.989                       | 5         |

Abbreviations: ADA, American Diabetes Association; NGT, normal glucose tolerance; NOS, Newcastle–Ottawa Scale.
Table 2 Meta-analysis of the *MTNR1B* rs10830963 polymorphism on GDM risk

| Subgroup       | Heterozygous (CG vs. CC) | Homozygous (GG vs. CC) | Allele model (G vs. C) |
|----------------|--------------------------|------------------------|-----------------------|
|                | Number of studies | Case/Control | OR (95% CI) | P\text{Effect} | Number of studies | Case/Control | OR (95% CI) | P\text{Effect} | Number of studies | Case/Control | OR (95% CI) | P\text{Effect} |
| Overall        | 14             | 3852/4736   | 1.29 (1.16–1.44) | <0.001               | 14             | 2628/2966   | 1.88 (1.55–2.27) | <0.001               | 14             | 10066/11228 | 1.37 (1.25–1.50) | <0.001               |
| Ethnicity      |                |             |              |                     |                |             |              |                     |                |             |              |                     |
| Asian          | 7              | 2271/2916   | 1.15 (1.02–1.28) | 0.020               | 7              | 1543/1796   | 1.52 (1.23–1.89) | <0.001               | 7              | 6026/7170   | 1.23 (1.10–1.37) | <0.001               |
| Caucasian      | 7              | 1681/1820   | 1.50 (1.31–1.72) | <0.001               | 7              | 1065/1170   | 2.45 (1.99–3.02) | <0.001               | 7              | 4040/4058   | 1.55 (1.41–1.71) | <0.001               |
Figure 1. Forest plot on the risk of GDM associated with rs10830963 (CG vs. CC)

Figure 2. Forest plot on the risk of GDM associated with rs10830963 (GG vs. CC)
Table 3 FPRP analysis for the significant associations of the MTNR1B rs10830963 C>G polymorphism and GDM risk

|                | OR (95%CI) | 0.25 | 0.1 | 0.01 | 0.001 | 0.0001 | 0.00001 |
|----------------|------------|------|-----|------|-------|--------|---------|
| **Overall**    |            |      |     |      |       |        |         |
| CG vs. CC      | 1.29 (1.16–1.44) | 0.002 | 0.005 | 0.056 | 0.375 | 0.857 | 0.984 |
| GG vs. CC      | 1.88 (1.55–2.27) | 0.002 | 0.007 | 0.070 | 0.433 | 0.884 | 0.987 |
| G vs. C        | 1.37 (1.25–1.50) | 0.001 | 0.004 | 0.038 | 0.286 | 0.800 | 0.976 |
| **Asian**      |            |      |     |      |       |        |         |
| CG vs. CC      | 1.15 (1.02–1.28) | 0.057 | 0.153 | 0.664 | 0.952 | 0.995 | 1.000 |
| GG vs. CC      | 1.52 (1.23–1.89) | 0.003 | 0.009 | 0.092 | 0.506 | 0.911 | 0.990 |
| G vs. C        | 1.23 (1.10–1.37) | 0.003 | 0.010 | 0.097 | 0.519 | 0.915 | 0.991 |
| **Caucasian**  |            |      |     |      |       |        |         |
| CG vs. CC      | 1.50 (1.31–1.72) | 0.002 | 0.007 | 0.074 | 0.446 | 0.889 | 0.988 |
| GG vs. CC      | 2.45 (1.99–3.02) | 0.016 | 0.047 | 0.351 | 0.845 | 0.982 | 0.998 |
| G vs. C        | 1.55 (1.41–1.71) | 0.002 | 0.006 | 0.056 | 0.375 | 0.857 | 0.984 |

Figure 3. Forest plot on the risk of GDM associated with rs10830963 (G vs. C)

In epidemiological research, it is necessary to clarify the general demographic characteristics, and we have also carried out extraction and display in Tables 1–3. For the mean pre-pregnancy body mass index (BMI) and mean age values with the subjects, we have re-extracted and supplemented in the Table 1. The mean age of cases/controls were 32.04/30.51 in subjects of Austria and 33.70/31.25 of Hungary. Meanwhile, the mean BMI of cases/controls were 28.31/23.40 in Austria and 26.78/23.32 in Hungary (Table 1).

Thank you very much again for Klara Rosta, M.D., Ph.D., Gábor Firneisz, M.D., Ph.D., et al.’s thoughtfulness and preciseness. Your comments mean a great deal to us. Next, we will improve our study work together with the editors of ‘Bioscience Reports’.
Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

Abbreviations
BMI, body mass index; CI, confidence interval; FPRP, false positive report probability; GDM, gestational diabetes mellitus; MAF, minor allele frequency; OR, odds ratio; SNP, single nucleotide polymorphism.

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