**SUPPLEMENTARY MATERIAL**

**Table S1.** Number of replicated and excluded samples due to low quality measurements.

|  |  |  |  |
| --- | --- | --- | --- |
| Gene | CpG | Replicated (included) samples (n) | Excluded samples (n) † |
| *HIF1A* | 1 | - | - |
| 2 | - | - |
| 3 | - | 1 |
| 4 | - | 1 |
| 5 | - | 1 |
| 6 | - | 1 |
| 7 | - | 1 |
| *EPO*  promoter | 1 | - | - |
| 2 | - | - |
| 3 | - | - |
| 4 | - | - |
| 5 | - | - |
| *EPO*  enhancer | 1 | - | - |
| 2 | - | - |
| 3 | - | - |
| *EPOR* | 1 | 2  2 | - |
| 2 | - |
| 3 | 2 | - |
| 4 | 2 | 3 |
| *VEGFA* | 1 | 2 | - |
| 2 | 2 | - |
| 3 | 2 | - |
| *BDNF* | 1 | - | - |
| 2 | - | - |
| 3 | - | 1 |
| 4 | - | 1 |
| 5 | - | 1 |
| *NTRK2* | 1 | - | - |
| 2 | - | - |
| 3 | - | - |
| 4 | - | 1 |
| 5 | - | 2 |
| 6 | - | 4 |
| 7 | *-* | *4* |
| 8 | *-* | *4* |
| 9 | *-* | *4* |
| † due to repeatedly low quality measurements (≥3 times). *BDNF*, brain-derived neurotrophic factor; CpG, 5’-cytosine-phosphate-guanine-3’ dinucleotide; df, degrees of freedom; *EPO*, erythropoietin; *EPOR*, erythropoietin receptor; *HIF1A*, hypoxia-inducible factor alpha; *NTRK2*, Neurotrophic Receptor Tyrosine Kinase 2; *VEGFA*, vascular endothelial growth factor A. | | | |

**Table S2.** Gestational and neonatal characteristics of children participating in this study and children lost-to-follow-up or declining participation.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | Children participating in this follow-up study  n = 21 | | Children lost to follow-up or declining participation  n = 20 | *p*-value |
| Gestational characteristics | | |  | |  |
|  | Maternal age (years) | 31.2 [24.9; 40.3] | | 29.9 [23.2; 40.3] | 0.413 |
|  | Maternal BMI | 25.0 [17.7; 36.0] | | 23.4 [18.8; 30.3] | 0.320 |
|  | Maternal smoking | 6 (29) | | 7 (35) | 0.658 |
|  | Preeclampsia | 4 (19) | | 4 (20) | 0.939 |
|  | HELLP | 2 (10) | | 1 (5) | 0.578 |
|  | PPROM | 2 (10) | | 0 (0) | 0.157 |
|  | Abnormal flow UA  (PI > 95th percentile or absent/reversed flow) | 14 (67) | | 12 (60) | 0.658 |
|  | Fetal brain-sparing  (CPR <1) | 8 (38) | | 6 (32) | 0.666 |
|  | Cesarean section | 15 (71) | | 11 (55) | 0.275 |
| Neonatal characteristics | |  | |  |  |
|  | Female | 12 (57) | | 10 (50) | 0.647 |
|  | Gestational age (weeks)† | 33.4 [28.0; 39.9] | | 37.4 [28.0; 39.6] | 0.267 |
|  | Birth weight (z-score)† | -2.62 [-4.66; -0.29] | | -2.64 [-5.94; 1.66] | 0.979 |
|  | Head circumference (z-score) | -1.97 [-3.62; -0.43] | | -2.20 [-4.31; -0.31] | 0.431 |
|  | Apgar score at 5 minutes† | 8 [4; 10] | | 9 [7; 10] | 0.050\* |
|  | Admission to NICU | 15 (71) | | 8 (40) | 0.043\* |
|  | Mechanical ventilation | 9 (43) | | 4 (20) | 0.116 |
|  | Bronchopulmonary dysplasia | 2 (10) | | 1 (5) | 0.578 |
|  | Necrotizing enterocolitis | 0 (0) | | 0 (0) | --- |
|  | Sepsis | 1 (5) | | 3 (15) | 0.269 |
|  | IVH/PVL | 0 (0) | | 0 (0) | --- |
|  | rcSO2 on postnatal day 1 | 80 [56; 92], n = 21 | | 80 [61; 95], n = 19 | 1.000 |
|  | rcSO2 on postnatal day 2 | 83 [64; 94], n = 18 | | 82 [68; 95], n = 19 | 0.710 |
|  | rcSO2 on postnatal day 3 | 81 [65; 93], n = 17 | | 80 [66; 92], n = 16 | 0.709 |
| Data are presented as mean/median [total range] or absolute number (percentage). †indicates, where a Mann-Whitney U test was used and a median is presented due to non-normality of the data. \* present differences between both groups at *p* ≤ 0.05. BMI, Body Mass Index; CPR, cerebroplacental ratio; HELLP, Syndrome of hemolysis, elevated liver enzymes, and low platelets; IVH, intraventricular hemorrhage; NICU, neonatal intensive care unit; PI, pulsatility index; PPROM, prolonged premature rupture of membranes (>12 hours); PVL, periventricular leukomalacia; rcSO2, regional cerebral oxygen saturation (measured with near-infrared spectroscopy); UA, umbilical artery. | | | | | |

**Table S3.** Correlation coefficients between the methylation levels of individual CpG sites per gene (location).

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Gene | CpG site | | | | | | | | |
| *HIF1A* |  | 1 | 2 | 3 | 4 | 5 | 6 |  |  |
| 2 | 0.064 | -- |  |  |  |  |  |  |
| 3 | -0.051 | 0.259 | -- |  |  |  |  |  |
| 4 | 0.005 | 0.468\* | 0.302 | -- |  |  |  |  |
| 5 | 0.268 | 0.423# | -0.108 | 0.350 | -- |  |  |  |
| 6 | 0.391# | 0.162 | 0.223 | 0.319 | 0.029 | -- |  |  |
| 7 | 0.264 | 0.549\* | 0.161 | 0.320 | 0.370# | 0.550\* |  |  |
| *EPO* promoter |  | 1 | 2† | 3 | 4† |  |  |  |  |
| 2† | 0.292 | -- |  |  |  |  |  |  |
| 3 | 0.353 | 0.278 | -- |  |  |  |  |  |
| 4† | 0.015 | 0.015 | 0.248 | -- |  |  |  |  |
| 5 | 0.500\* | 0.520\* | 0.214 | -0.090 |  |  |  |  |
| *EPO* enhancer |  | 1 | 2 |  |  |  |  |  |  |
| 2 | 0.457\* | -- |  |  |  |  |  |  |
| 3 | 0.510\* | 0.848\* |  |  |  |  |  |  |
| *EPOR* |  | 1 | 2 | 3† |  |  |  |  |  |
| 2 | 0.631\* | -- |  |  |  |  |  |  |
| 3† | 0.598\* | 0.474\* | -- |  |  |  |  |  |
| 4 | -0.089 | -0.174 | 0.492\* |  |  |  |  |  |
| *VEGFA* |  | 1 | 2 |  |  |  |  |  |  |
| 2 | -0.077 | -- |  |  |  |  |  |  |
| 3 | 0.006 | 0.025 |  |  |  |  |  |  |
| *NTRK2* |  | 1 | 2† | 3† | 4† | 5 | 6 | 7 | 8† |
| 2† | 0.426\* | -- |  |  |  |  |  |  |
| 3† | 0.140 | 0.411# | -- |  |  |  |  |  |
| 4† | 0.492\* | 0.432# | 0.270 | -- |  |  |  |  |
| 5 | -0.235 | 0.160 | 0.270 | 0.393# | -- |  |  |  |
| 6 | 0.144 | 0.287 | 0.236 | 0.394 | 0.607\* | -- |  |  |
| 7 | 0.273 | 0.416# | 0.066 | 0.411# | 0.254# | 0.416# | -- |  |
| 8† | -0.150 | 0.093 | -0.259 | 0.565\* | 0.572\* | 0.630\* | 0.328 | -- |
| 9 | 0.554\* | 0.523\* | -0.133 | 0.418\* | 0.243 | 0.507\* | 0.535\* | 0.426# |
| *BDNF* |  | 1 | 2 | 3 | 4† |  |  |  |  |
| 2 | 0.901\* | -- |  |  |  |  |  |  |
| 3 | 0.679\* | 0.686\* | -- |  |  |  |  |  |
| 4† | 0.582\* | 0.550\* | 0.400# | -- |  |  |  |  |
| 5 | 0.395# | 0.335 | 0.584\* | 0.422# |  |  |  |  |
| †Spearman’s rank correlation analysis was used due to non-normality of the data. # and \* mark correlations at *p* < 0.1 and *p* < 0.05, respectively. *BDNF*, brain-derived neurotrophic factor; CpG, 5’-cytosine-phosphate-guanine-3’ dinucleotide; *EPO*, erythropoietin; *EPOR*, erythropoietin receptor; *HIF1A*, hypoxia-inducible factor alpha; *NTRK2*, neurotrophic tyrosine kinase, receptor, type 2; *VEGFA*, vascular endothelial growth factor A. | | | | | | | | | |