**SUPPLEMENTAL FILE**

**Figures**

**Supplemental Figure 1: *IRS4* expression in brain and pituitary**. RT-PCR amplification of IRS4 in three individuals from the indicated tissues or brain nuclei. The expected product is 198 bp. Abbreviations: INF, infundibular nucleus; LH, lateral hypothalamus; PIT, pituitary; PVN, paraventricular nucleus; SON, supraoptic nucleus. No bands were seen when PCR was performed on samples in which the RT enzyme was omitted (not shown).

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**Supplemental Figure 2: Characterization of the HPT-axis in male and female wild type and *Irs4* null mice**.   
(A) *Trh* mRNA expression in the paraventricular nucleus of the hypothalamus, measured as the integrated density of the X-ray film signal,1 and (B) pituitary *Tshb* mRNA expression. (C) serum TSH, (D) T4, and (E) T3 concentrations. Black and white bars represent wild-type (WT) and knock out (KO) mice, respectively. Means with SEM are presented. P-values indicate the results of the two-way ANOVA. Post-hoc pair wise comparisons between groups are presented with the following symbols (a P<0.05, \*\*P<0.01).

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**Tables**

**Supplemental Table 1** **TRH stimulation testing of individuals with *IRS4* mutations.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case** | **M/F** | **Age at testing (years)** | **Baseline TSH (mU/L)** | **Peak TSH (mU/L)** | **Time peak TSH (minutes after TRH infusion)** | **Normalised TSH (mU/L)** | **Time normalised TSH (minutes after TRH infusion)** | **Baseline PRL (µg/L)** | **Peak PRL (µg/L)** |
| **A.II.6** | F | 50 | 3.0 | 22.5 | 20 min | 10.7 b | 120 min | 8.0 | 35.0 |
| **A.III.4** | M | 2 mos | 3.2 | 9.2\* | 40 min | 4.4 | 180 min | 12.5 | 48.0 |
| **A.III.5** | M | 2 weeks | 4.6 | 10.9\* | 30 min | 4.6 | 180 min | 72\* | 125\* |
| **B.II.2** | F | 53 | 1.5 | 11.0 | 20 min | 4.5 | 120 min | 4.5 | 49.0 |
| **B.III.2** | F | 26 | 3.6 | 21.9 | 20 min | 11.1b | 120 min | 11.5 | 88.0 |
| **B.III.3** | M | 11 | 3.4 | 3.9\* | 45 min | 3.1 | 120 min | 4.3 | x |
| **B.III.4** | M | 1 mos | 4.5 | 8.3\* | 30 min | 3.8 | 120 min | 9.1 | x |
| **C.I.2** | F | 53 | 3.5 | 22.9\* | 20 min | 8.0b | 120 min | 4.5 | 53.0 |
| **C.II.2** | F | 31 | 1.3 | 9.3 | 20 min | 4.6 | 90 min | 9.5 | 36.0 |
| **C.III.2** | M | 2 mos | 8.3 | 16.8 | 30 min | 8.1 | 120 min | 23.5 | x |
| **D.II.4** | F | 37 | 2.2 | 18.0 | 20 min | 6.6 b | 120 min | 14.5 | 75.0 |
| **D.II.6** | F | 35 | 1.1 | 10.8 | 20 min | 4.7 | 120 min | 6.5 | 38.0 |
| **D.III.6** | M | 3 weeks | 3.5 | 5.2\* | 30 min | 3.5 | 120 min | 34.2\* | 61.0 |
| **E.II.4a** | F | 35 | 0.7 | 8.9 | 60 min\* | 4.9 | 120 min | 38.0\* | 205.0 |
| **E.III.4** | M | 2 weeks | 2.8 | 9.8\* | 20 min | 3.4 | 180 min | x | x |

\*: abnormal values; a, Lactating woman; b, lowest measured TSH concentration. Interpretation of TSH in adults: maximum response of TSH to TRH 2.8-22.5 mU/L,2 a peak TSH threefold the baseline TSH, and TSH after 20 min higher than after 60 min,3 in infants: maximum response of TSH to TRH >15 mU/L and return to baseline within 3 hours.4 Reference interval of baseline PRL in males: 0-19 µg/L, and in females: 0-25 µg/L (in-house reference interval). Minimum response of PRL to TRH >2.5-fold increase.5 Abbreviations: F, female; M, male; min, minutes; mos, months; PRL, prolactin; TSH, thyroid stimulating hormone; x, missing value.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case** | **M/F** | **Age (yr)** | **LT4 treat-ment** | **Time of blood withdrawal** | **GH (mU/L)** | **IGF-1 (nmol/L)** | **IGF-1 (SDS)** | **IGFBP3**  **(mg/L)** | **Height (cm; SDS)** | **Weight (kg; SDS)** | **BMI** |
| **A.II.6** | F | 50 | - | 08:30 | 1.1  (<20) | 25 | +1.0 | 2.7  (1.0-4.0) | 171.3  (+0.1) | 52.7  (-1.6) | 18.0 kg/m2 |
| **A.III.4** | M | 19 | + | 08:30 | 0.7  (<10) | 35 | +0.7 | 2.3  (1.5-6.1) | 173  (-1.5) | 59.1  (-1.7) | 19.8 kg/m2 |
| **A.III.5** | M | 15 | + | 08:59 | 2.4  (<10) | 82 | +3.1 | 3.2  (1.5-6.1) | 182.3  (+0.6) | 62.9  (+0.1) | 18.9  kg/m2 |
| **B.II.2** | F | 53 | - | 09:40 | 1.8  (<20) | 28 | +1.6 | 2.3  (1.0-4.0) | 167.2  (-0.6) | 62.9  (-0.1) | 22.5  kg/m2 |
| **B.III.2** | F | 26 | - | 09:06 | 31.0\*  (<20) | 32 | +1.1 | 1.7  (1.5-6.0) | 169.2  (-0.2) | 57.6  (-0.8) | 20.2  kg/m2 |
| **B.III.3** | M | 23 | + | 10:26 | 19.0\*  (<10) | 45 | +2.8 | 2.5  (1.5-6.0) | 184.4  (+0.1) | 70.5  (-0.5) | 20.7  kg/m2 |
| **B.III.4** | M | 13 | + | 10:27 | 20.0\*  (<10) | 62 | +1.5 | 2.6  (1.4-6.5) | 165.8  (+0.3) | 51.0  (+0.3) | +0.5  SDS |
| **C.I.2** | F | 53 | - | 10:12 | <0.2  (<20) | 12 | -1.2 | 3.5  (1.0-4.0) | 167.5  (-0.5) | 86.5\*  (+2.0) | 30.8 kg/m2 |
| **C.II.2** | F | 31 | - | 10:19 | 1.4  (<20) | 37 | +2.3 | 2.7  (1.0-4.5) | 173.8  (+0.5) | 82.7  (+1.7) | 27.4  kg/m2 |
| **C.III.2** | M | 6 | + | 10:41 | 2.1  (<10) | 20 | +1.0 | 2.5  (1.2-4.0) | 117.5  (-0.5) | 22.7  (+0.1) | +1.0 SDS |
| **D.II.4** | F | 37 | - | 08:12 | 1.7  (<20) | 30 | +1.3 | 1.9  (1.0-4.5) | 173.5  (+0.4) | 66.7  (+0.3) | 22.2  kg/m2 |
| **D.II.6** | F | 35 | - | 08:48 | 0.6  (<20) | 27 | +0.8 | 2.2  (1.0-4.5) | 173.5  (+0.4) | 55.8  (-1.1) | 18.5  kg/m2 |
| **D.III.6** | M | 1 | + | 08:32 | 6.5  (<10) | 6.7 | +1.0 | 2.4  (1.0-3.2) | 79  (+0.5) | 10.2  (-0.2) | -0.8 SDS |
| **E.II.4a** | F | 35 | - | 10:37 | 0.8  (<20) | 19 | -0.6 | 2.2  (1.0-4.5) | 172.2  (+0.2) | 67.3  (+0.4) | 22.7  kg/m2 |
| **E.III.4** | M | 5 | + | 08:07 | 20\*  (<10) | 15 | +0.6 | 1.7  (1.0-3.2) | 116.8  (-0.1) | 22.8  (+0.5) | +1.2 SDS |
| **E.III.5** | M | 3 | - | 09:02 | 14\*  (<10) | 10 | +0.7 | 1.6  (1.0-3.2) | 102.9  (-0.3) | 18.5  (+0.7) | +1.5 SDS |
| **E.III.6** | F | 5 mos | - | 09:02 | 8.5  (<20) | 6.0 | x | 1.1  (0.6-3.6) | x | 6.4  (-1.3) | -1.3 SDS |

**Supplemental Table 2** **Growth hormone concentrations in individuals carrying *IRS4* mutations.**

\*: abnormal values; a, Lactating woman. Abbreviations: cm, centimetres; F, female; GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP3, insulin-like growth factor-binding protein 3; kg, kilograms; M, male; mos, months; SDS, standard deviation score; x, missing value; yr, years; +, yes; -, not applicable. Age specific reference intervals for IGFBP-3 and GH (in-house) between parentheses. IGF-1 SDS relative to age and gender.6 BMI expressed as kg/m2 in adults, and SDS in children. Height, weight and BMI SDS calculated with Dutch reference data.7

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case** | **M/F** | **Age (yr)** | **LT4 treat-ment** | **Time of blood with-drawal** | **Fasting glucose (mmol/L) RI <5.6** | **Leptin**  **(ng/mL)** | **T3/T4 ratiob (11.99-22.19)** | **rT3 (nmol/L)**  **RI: 0.11-0.44** | **Tg (pmol/L)**  **RI: <60** | **ACTH (ng/L)**  **RI: 0-55** | **Cortisol (nmol/L) RI: 100-650** | **PRL (µg/L)** | **LH (U/L)** | **FSH (U/L)** | **Test (nmol/L)** | **Estr (nmol/L)** | **SHBG (nmol/L)** |
| **A.II.6** | F | 50 | - | 08:30 | 5.2 | 3.0  (1.6-11.1) | 20.04 | 0.27 | 4 | 45 | 499 | 11.0  (0-25) | 43.0\*  (2.0-26.2) | 60.68\*  (2.2-17.0) | x | <0.02\*  (0.1-1.1) | 107  (40-120) |
| **A.III.4** | M | 19 | + | 08:30 | 5.1 | 3.2  (0.8-4.3) | 30.07\* | 0.08\* | 3 | 53 | 323 | 12.0 (0-19) | 6.8  (1.95-9.4) | 3.04  (1.39-8.9) | 17.9  (11.6-33.8) | x | 29  (13.1-53.2) |
| **A.III.5** | M | 15 | + | 08:59 | 5.0 | 6.5  (0.6-24.7) | X | 0.23 | 10 | 22 | 218 | 6.0 (0-19) | 2.5  (<0.1-3.7) | 1.45  (<0.1-8.6) | 9.9  (1.1-25.4) | x | 30  (16-100) |
| **B.II.2** | F | 53 | - | 09:40 | 5.2 | 31.6\*  (3.2-22.1) | 18.16 | 0.27 | 25 | <5 | 162 | 6.0 (0-25) | 46.1\*  (2.0-26.2) | 138.80\*  (2.2-17.0) | x | <0.02\*  (0.1-1.1) | 25  (40-120) |
| **B.III.2** | F | 26 | - | 09.02 | 4.6 | 10.6  (2.2-14.9) | 16.27 | 0.36 | <1 | 10 | 192 | 11.5 (0-25) | 11.7  (2.0-26.2) | 3.84  (2.2-17.0) | x | 0.35  (0.1-1.1) | 61  (40-120) |
| **B.III.3** | M | 23 | + | 10:26 | 4.0 | 2.6  (0.9-5.2) | X | 0.06\* | 16 | 10 | 164 | 5.5 (0-19) | 12.4\*  (1.95-9.4) | 25.89\*  (1.39-8.9) | 17.7  (11.6-33.8) | x | x |
| **B.III.4** | M | 13 | + | 10:27 | 5.4 | 2.9  (0.9-34.7) | X | 0.22 | 22 | 18 | 168 | 5.5 (0-19) | 3.1  (<0.1-3.7) | 10.59\*  (<0.1-8.6) | 8.6  (0.1-21.5) | x | x |
| **C.I.2** | F | 53 | - | 10:12 | 5.5 | 52.7\*  (7.5-51.2) | 22.49\* | 0.26 | 14 | 13 | 255 | 5.5 (0-25) | 39.5\*  (2.0-26.2) | 55.70\*  (2.2-17.0) | x | 0.03\*  (0.1-1.1) | 32  (40-120) |
| **C.II.2** | F | 31 | - | 10:19 | 5.4 | 29.7  (5.1-34.7) | 18.43 | 0.25 | 11 | 10 | 204 | 7.5 (0-25) | 5.7  (2.0-26.2) | 5.08  (2.2-17.0) | x | 0.15  (0.1-1.1) | 20  (40-120) |
| **C.III.2** | M | 6 | + | 10.41 | 4.5 | 3.9  (0.4-11.0) | 33.52\* | 0.28 | 2 | 20 | 255 | 12.5 (0-19) | <1.0  (<0.1-4.0) | <1.00  (<0.1-7.1) | <0.1  (<0.5) | x | x |
| **D.II.4** | F | 37 | - | 08:12 | 5.2 | 12.7  (2.8-19.5) | 18.73 | 0.24 | 23 | 18 | 361 | 18.5 (0-25) | 5.0  (2.0-26.2) | 3.01  (2.2-17.0) | x | 0.43  (0.1-1.1) | 82  (40-120) |
| **D.II.6** | F | 35 | - | 08:48 | 5.1 | 7.8  (1.6-11.1) | 16.76 | 0.28 | 12 | 14 | 248 | 7.5 (0-25) | 6.4  (2.0-26.2) | 6.5  (2.2-17.0) | x | 0.28  (0.1-1.1) | x |
| **D.III.6** | M | 1 | + | 08:32 | 4.7 | 6.4  (0.3-4.1) | X | 0.43 | 7.6 | 135\* | 420 | 728\* (0-19) | 1.4  (<0.1-4.0) | 1.1  (<0.1-7.1) | <0.1  (<1.3) | x | x |
| **E.II.4a** | F | 35 | - | 10:37 | 4.7 | 14.0  (3.2-22.1) | 17.22 | 0.19 | 12 | 14 | 203 | 31.0\* (0-25) | 1.4  (2.0-26.2) | 6.50  (2.2-17.0) | x | 0.08\*  (0.1-1.1) | 56  (40-120) |
| **E.III.4** | M | 5 | + | 08:07 | 4.1 | X | 19.72 | 0.22 | 12 | 21 | 326 | 25.0\* (0-19) | <1.0  (<0.1-4.0) | <1.00  (<0.1-7.1) | <0.1  (<0.7) | x | x |
| **E.III.5** | M | 3 | - | 09:02 | 4.0 | 2.9  (0.4-3.0) | 22.21\* | 0.20 | 6 | 25 | 249 | 9.5 (0-19) | <1.0  (<0.1-4.0) | <1.00  (<0.1-7.1) | <0.1  (<0.5) | x | x |
| **E.III.6** | F | 5 mos | - | 09:02 | 5.4 | 7.2\*  (0.8-2.4) | 23.04\* | 0.51 | 48 | 86\* | 103 | 21.0 (0-25) | <1.0  (<0.1-3.3) | 5.67  (<0.1-7.1) | x | 0.03  (<0.07-0.2) | 168  (60-252) |

**Supplemental Table 3** **Endocrine parameters in individuals carrying *IRS4* mutations.**

\*: abnormal values; a, Lactating woman. b, units used in ratio calculation: T3, ng/dL; T4, ug/dL. Abbreviations: ACTH, adrenocorticotropic hormone; Estr, 17β-estradiol; F, female; FSH, follicle stimulating hormone; LH, luteinizing hormone; M, male; mos, months; PRL, prolactin; RI, reference interval; SHBG, sex hormone-binding globulin; T3, triiodothyronine; T4, thyroxin; TBG, thyroxine-binding globulin; Test, testosterone; Tg, thyroglobulin; rT3, reverse T3; x, missing value; yr, years; +, yes; -, not applicable. Reference intervals for leptin (age specific for children, BMI specific for adults),8-10 17β-estradiol, FSH, LH, SHBG, and testosterone (females and males, age specific) 11-14 , and T3/T4 ratio15 between parentheses.

**Supplemental Table 4** **Oral glucose tolerance tests in individuals with *IRS4* mutations.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Case** | **M/F** | **Age** | **Baseline FPG (mmol/L)** | **Second FPG**  **(mmol/L)** | **PG after 2 hours**  **(mmol/L)** |
| **A.II.6** | F | 50 | 5.2 | 5.2 | 7.3 |
| **A.III.4** | M | 19 | 5.1 | 5.0 | 6.1 |
| **A.III.5** | M | 15 | 5.0 | 5.1 | 6.2 |
| **B.II.2** | F | 53 | 5.2 | 5.3 | 7.3 |
| **B.III.2** | F | 26 | 4.6 | 4.4 | 4.9 |
| **B.III.3** | M | 23 | 4.0 | 4.5 | 4.2 |
| **B.III.4** | M | 13 | 5.4 | 5.4 | 5.6 |
| **C.I.2** | F | 53 | 5.5 | 5.5 | 6.3 |
| **C.II.2** | F | 31 | 5.4 | 5.2 | 6.0 |
| **C.III.2** | M | 6 | 4.5 | x | 5.6 |
| **D.II.4** | F | 37 | 5.4 | 5.2 | 5.7 |
| **D.II.6** | F | 35 | 5.1 | 5.2 | 3.5 |
| **E.II.4 a** | F | 35 | 4.5 | 4.7 | 7.4 |

\*: abnormal values; a, Lactating woman. Abbreviations: F, female; FPG, fasting plasma glucose; M, male; PG, plasma glucose; x, missing value. Reference interval for FPG ≤5.6 mmol/L, PG after two hours ≤7.8.16

**Supplemental Table 5** **HOMA in individuals with *IRS4* mutations.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Case** | **M/F** | **Age (years)** | **FPI (pmol/L)** | **FPI (mU/L)** | **FPG (mmol/L)** | **HOMA-IR** |
| **A.II.6** | F | 50 | 22 | 3.2 | 5.2 | 0.74 (1.85) |
| **A.III.4** | M | 19 | 62 | 8.9 | 5.1 | 2.02 (2.17) |
| **A.III.5** | M | 15 | 28 | 4.0 | 4.3 | 0.76 (3.16) |
| **B.II.2** | F | 53 | 105\* | 15.1 | 4.9 | 3.29 (1.85) \* |
| **B.III.2** | F | 26 | 58 | 8.4 | 4.4 | 1.64 (1.85) |
| **B.III.3** | M | 23 | 27 | 3.9 | 4.1 | 0.71 (2.17) |
| **B.III.4** | M | 13 | 37 | 5.3 | 4.5 | 1.06 (3.16) |
| **C.I.2** | F | 53 | 99\* | 14.3 | 5.5 | 3.50 (1.85) \* |
| **C.II.2** | F | 31 | 145\* | 20.9 | 5.1 | 4.74 (1.85) \* |
| **C.III.2** | M | 6 | 25 | 3.6 | 4.5 | 0.72 (3.16) |
| **D.II.4** | F | 37 | 16 | 2.3 | 5.9\* | 0.60 (1.85) |
| **D.II.6** | F | 36 | <15 | <2.2 | 4.6 | 0.45 (1.85) |
| **D.III.6** | M | 2 | <15 | <2.2 | 4.7 | 0.46 (3.16) |
| **E.II.4a** | F | 35 | 40 | 5.8 | 4.8 | 1.24 (1.85) |
| **E.III.4** | M | 5 | <15 | <2.2 | 4.9 | 0.48 (3.16) |
| **E.III.5** | M | 3 | <15 | <2.2 | 4.8 | 0.47 (3.16) |
| **E.III.6** | F | 5 mos | <15 | <2.2 | 3.4 | 0.33 (3.16) |

\*: abnormal values. Abbreviations: F, female; FPG, fasting plasma glucose; FPI, fasted plasma insulin; HOMA, homeostatic model assessment; IR, insulin resistance; M, male; mos, months; x, missing value. Reference interval for FPG ≥5.6 mmol/L, and FPI <62.5 pmol/L (American Diabetes Association). HOMA-IR is defined as FPG (mmol/L) x FPI (mU/L)/22.5. Cut-off values for HOMA-IR are presented in parentheses.17 18

**Supplemental Table 6.** **Lipid spectrum of individuals (male and female) with *IRS4* mutations.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Case** | **M/F** | **Age (years)** | **TC (mmol/L)** | **HDL (mmol/L)** | **LDL (mmol/L)** | **TG (mmol/L)** |
| **A.II.6** | F | 50 | 7.24\* | 1.43 | 5.11\* | 1.55 |
| **A.III.4** | M | 19 | 3.58 | 1.16 | 2.07 | 0.77 |
| **A.III.5** | M | 15 | 3.27 | 1.14 | 1.96 | 0.38 |
| **B.II.2** | F | 53 | 6.47\* | 1.56 | 4.61\* | 0.67 |
| **B.III.2** | F | 26 | 3.52 | 0.92\* | 2.37 | 0.51 |
| **B.III.3** | M | 23 | 4.21 | 1.07 | 2.89 | 0.55 |
| **B.III.4** | M | 13 | 4.30 | 1.85 | 2.33 | 0.26\* |
| **C.I.2** | F | 53 | 7.99\* | 1.87 | 4.58\* | 3.43\* |
| **C.II.2** | F | 31 | 4.60 | 1.80 | 2.41 | 0.87 |
| **D.II.4** | F | 37 | 4.12 | 1.79 | 2.11 | 0.48 |
| **D.II.6** | F | 36 | 3.86 | 1.44 | 2.05 | 0.83 |
| **D.III.6** | M | 2 | 4.11 | 0.98\* | 2.74 | 1.57 |
| **E.II.4a** | F | 35 | 4.81 | 1.49 | 3.16 | 0.36\* |
| **E.III.4** | M | 5 | 3.63 | 1.60 | 1.94 | 0.20\* |
| **E.III.5** | M | 3 | 4.37 | 1.27 | 2.93 | 0.37 |
| **E.III.6** | F | 5 mos a | 4.00 | 0.97\* | 1.69 | 2.97\* |

\*: abnormal values; a Most likely non-fasting measurements. Abbreviations: F, female; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M, male; mo, months; TC, total cholesterol; TG, triglyceride; x, missing value; y, years. Paediatric reference intervals for total cholesterol: 2.7-5.5 mmol/L, HDL: 1.0-2.3 mmol/L, LDL: 1.1-3.4 mmol/L, triglycerides: 0.34-1.95 mmol/L.19 Adult reference intervals for total cholesterol: 2.9-6.1 mmol/L, HDL: 1.0-2.7 mmol/L, LDL: 1.2-4.3 mmol/L, triglycerides: 0.45-2.60 mmol/L.19

**Supplemental Table 7:** **TSH secretion characteristics.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **TSH** | | |
|  | **Patients** | **Controls** | **P** |
| **Number** | 2 | 11 |  |
| **Age (years)** | 21.0 | 33.0 (30.0-37.0) | 0.005 |
| **BMI (kg/m2)** | 20.4 | 23.4 (21.6-27.2) | 0.112 |
| **Free T4 (pmol/L)** | 3.4 | 16.6 (14.6-19.3) | 0.000 |
| **Pulse frequency (number/24 hours)** | 20.5 | 18.0 (17.0-21.0) | 0.377 |
| **Fast half-life (min)** | 9.6 | 21.4 (12.9-26.9) | 0.140 |
| **Slow half-life (min)** | 108.0 | 84.0 (55.4-89.0) | 0.146 |
| **Mode day (min)** | 7.4 | 17.2 (14.2-30.0) | 0.083 |
| **Mode night (min)** | 23.2 | 9.6 (8.3-14.8) | 0.060 |
| **Basal secretion (mU/L/24 hours)** | 2.2 | 23.0 (9.3-34.6) | 0.030 |
| **Pulsatile secretion (mU/L/24 hours)** | 2.6 | 21.9 (14.3-30.8) | 0.032 |
| **Total secretion (mU/L/24 hours)** | 4.7 | 43.6 (33.5-62.1) | 0.015 |
| **Mean pulse mass (mU/L)** | 0.1 | 1.3 (0.9-1.8) | 0.095 |
| **Weibull lambda (number/24 hours)** | 18.5 | 16.6 (15.8-17.9) | 0.359 |
| **Weibull gamma** | 2.0 | 2.1 (1.8-2.4) | 0.642 |
| **Approximate entropy** | 0.9 | 0.9 (0.6-1.2) | 0.846 |

Data are presented as median, or median (interquartile range).

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