**SUPPLEMENTARY TABLES**

**Supplementary Table 1. SNPs genotyped in the *INSR, TOX3, YAP1*, *HMGA1*, and *ERBB3* genes.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **db SNP ID** | **Variation Type** | **Chromosome location (GRCh38)** | **Nucleotide change** | **Type** | **Ref Allele\*** | **Alt Allele\*** |
| *INSR* | rs2059807 | SNV Single Nucleotide Variation | 19:7166098 | A>G,T | Intron Variant | A=0.5178 | G=0.4822, T=0.0000 |
| *TOX3* | rs4784165 | SNV Single Nucleotide Variation | 16:52313907 | T>A,G | Intron Variant | T=0.764 | A=0.000, G=0.236 |
| *YAP1* | rs1894116 | SNV Single Nucleotide Variation | 11:102199908 | A>G | Intron Variant | A=0.9575 | G=0.0425 |
| *HMGA2* | rs2272046 | SNV Single Nucleotide Variation | 12:65830681 | A>C | Intron Variant | A=0.992 | C=0.008 |
| *ERBB3* | rs2292239 | SNV Single Nucleotide Variation | 12:56088396 | T>C,G | Intron Variant | T=0.2110 | C=0.0000, G=0.7890 |

\*Frequency for Latin American individiuals with mostly European and Native American Ancestry. Identifiers: BioSample: SAMN10492700; Sample name: Latin American 2 (Available in https://www.ncbi.nlm.nih.gov/snp/)

**Supplementary Table 2. Clinical and endocrine-metabolic parameters of women with PCOS according to the overdominant model of rs2059807 in *INSR* gene.**

|  |  |  |  |
| --- | --- | --- | --- |
| rs2059807 | | | |
|  | **GG+AA** | **GA** | **P-value** |
| **Case number** | 27 | 22 |  |
| **Age (years)** | 29 (24-34) | 26.5 (22-31.25) | 0.141\* |
| **Weight (kg)** | 64 (56-75) | 8.5 (55-74.5) | 0.5\* |
| **Height (m)** | 1.64 ± 0.06 | 1.6 ± 0.06 | **0.019\*** |
| **BMI (kg/m2)** | 23.17 (21.48-25.39) | 23.69 (21.28-28.17) | 0.872\* |
| **Menarche (years)** | 13 (12-14) | 13 (12-14) | 0.421\* |
| **Menstrual cycle (days)** | 30.50 (29.50-48.75) | 31 (28.5-35) | 0.941\* |
| **Menstrual cycle length (days)** | 5 (4-8) | 4 (3.75-5.25) | 0.121\* |
| **FSH (mUl/ml)** | 4.9 (2.56-8.82) | 6.26 (3.59-9.05) | 0.291\* |
| **AMH (ng/ml)** | 7.02 (5.11-12.6) | 8.58 (4.85-12.32) | 0.688\* |
| **LH (mUl/ml)** | 5.42 (2.7-9.7) | 7.15 (5.77-12.02) | 0.082\* |
| **LH/FSH ratio** | 1.22 (0.81-1.73) | 1.4 (0.85-1.82) | 0.366\* |
| **TSH (mUl/ml)** | 1.63 (1.26-2.86) | 1.7 (1.33-2.48) | 0.912\* |
| **E2 (pg/ml)** | 67.15 (41.25-125) | 48.8 (28.95-63.12) | 0.094\* |
| **Androstenedione (ng/ml)** | 1.62 ± 0.63 | 1.37 ± 0.52 | 0.072\*\* |
| **DHEAS (ug/dL)** | 148.22 ± 64.13 | 162.41 ± 64.25 | 0.223\*\* |
| **Free testosterone (pg/ml)** | 1.79 (0.89-2.96) | 1.32 (0.93-1.67) | 0.421\* |
| **Fasting insulin (uUl/ml)** | 5.72 (2.62-10.03) | 4.14 (2.1-8.46) | 0.512\* |
| **Post meal insulin (uUl/ml)** | 25.1 (8.84-49.2) | 29.9 (16.2-43.6) | 0.587\* |
| **Fasting blood glucose (mg/dL)** | 85.99 ±7.98 | 81.18 ± 8.71 | **0.025\*\*** |
| **Post meal glucose (mg/dL)** | 84 (76-96) | 78 ( 65.75-90) | 0.184\* |
| **HOMA-IR** | 1.14 (0.55-2.12) | 0.83 (0.47-1.69) | 0.456\* |
| **HOMA-IS** | 0.039 (0.021-0.08) | 0.05 (0.03-0.09) | 0.456\* |
| **Glycosylated hemoglobin (%)** | 5.16 (4.89-5.52) | 5.39 (5.07-5.88) | 0.252\* |
| **Total ovarian volume (cm3)** | 13.2 (10.52-17.77) | 11.82 (9.23-19.57) | 0.741\* |
| **Total AFC (number of follicles)** | 25.5 (21-31) | 33 (25.25-36.75) | **0.039\*** |

BMI: Body mass index; FSH: Follicle stimulating hormone; AMH: Anti-Müllerian hormone; LH: Luteinizing hormone; TSH: Thyroid-Stimulating hormone; E2: Estradiol; DHEAS: Dehydroepiandrosterone sulfate; HOMA-IR: Homeostasis model assessment-Insulin resistance; HOMA-IS: Homeostasis model assessment-Insulin sensitive; AFC: Antral follicular count.

\*Mann-Whitney U-test (no-continuous variables). Data are expressed as median (interquartile range).

\*\* Student's t-test (continuous variables). Data are expressed as mean ± standard deviation.

**Supplementary Table 3. Clinical and endocrine-metabolic parameters of women with PCOS according to the recessive model of rs4784165 in *TOX3* gene.**

|  |  |  |
| --- | --- | --- |
| rs4784165 | | |
|  | **TT+GT** | **TT** |
| **Case number** | 48 | 1 |
| **Age (years)** | 28 (23.25-32) | 40 |
| **Weight (kg)** | 60 (55-72.75) | 87 |
| **Height (m)** | 1.62 ± 0.06 | 1.63 |
| **BMI (kg/m2)** | 23.16 (21.48-25.38) | 32.75 |
| **Menarche (years)** | 13 (12-14) | 13 |
| **Menstrual cycle (days)** | 31 (29-42) | 45 |
| **Menstrual cycle length (days)** | 5.0 (4.0-8.0) | 5 |
| **FSH (mUl/ml)** | 5.81 (2.61-8.86) | 4.9 |
| **AMH (ng/ml)** | 8.13 (5.05-12.58) | 7.77 |
| **LH (mUl/ml)** | 6.87 (4.53-10.35) | 5.42 |
| **LH/FSH ratio** | 1.31 (0.85-1.76) | 1.11 |
| **TSH (mUl/ml)** | 1.67 (1.29-2.73) | 2.49 |
| **E2 (pg/ml)** | 52.7 (31.8-72.9) | 71.6 |
| **Androstenedione (ng/ml)** | 1.52 ± 0.60 | 0.91 |
| **DHEAS (ug/dL)** | 156.9 ± 62.46 | 43 |
| **Free testosterone (pg/ml)** | 1.36 (0.92-2.41) | 0.72 |
| **Fasting insulin (uUl/ml)** | 4.68 (2.48-8.86) | 9.95 |
| **Post meal insulin (uUl/ml)** | 28.8 (13.35-44.35) | 19.6 |
| **Fasting blood glucose (mg/dL)** | 83.58 ± 8.48 | 96.0 |
| **Post meal glucose (mg/dL)** | 80.0 (71.5-95.0) | 84.0 |
| **HOMA-IR** | 0.90 (0.54-1.95) | 2.36 |
| **HOMA-IS** | 0.05 (0.02-0.08) | 0.02 |
| **Glycosylated hemoglobin (%)** | 5.24 (5.03-5.76) | 5.5 |
| **Total ovarian volume (cm3)** | 12.2 (9.6-18.0) | 19.3 |
| **Total AFC (number of follicles)** | 28.0 (23.5-35.0) | 23.0 |

BMI: Body mass index; FSH: Follicle stimulating hormone; AMH: Anti-Müllerian hormone; LH: Luteinizing hormone; TSH: Thyroid-Stimulating hormone; E2: Estradiol; DHEAS: Dehydroepiandrosterone sulfate; HOMA-IR: Homeostasis model assessment-Insulin resistance; HOMA-IS: Homeostasis model assessment-Insulin sensitive; AFC: Antral follicular count.

**Supplementary Table 4. Clinical and endocrine-metabolic parameters of women with PCOS according to the genotypes of rs1894116 in *YAP1* gene.**

|  |  |  |  |
| --- | --- | --- | --- |
| rs1894116 | | | |
|  | **AA** | **GA** | **P-value** |
| **Case number** | 46 | 3 |  |
| **Age (years)** | 28 (23-32.25) | 30 (27-NR) | 0.427\* |
| **Weight (kg)** | 61 (55.75-75) | 55 (52-NR) | 0.175\* |
| **Height (m)** | 1.62 ± 0.07 | 1.67 ± 0.02 | 0.904\* |
| **BMI (kg/m2)** | 23.2 (21.48-25.91) | 19.72 (18.21-NR) | 0.095\* |
| **Menarche (years)** | 13 (12-14) | 13 (12-NR) | 0.684\* |
| **Menstrual cycle (days)** | 31 (30-45) | 30 (28-NR) | 0.495\* |
| **Menstrual cycle length (days)** | 5 (4-8) | 4 (4-NR) | 0.459\* |
| **FSH (mUl/ml)** | 5.27 (2.56-8.75) | 9.71 (8.61-NR) | 0.091\* |
| **AMH (ng/ml)** | 7.9 (5-12.5) | 9.83 (5.15-NR) | 0.588\* |
| **LH (mUl/ml)** | 6.75 (4.57-10.5) | 8.1 (2.7-NR) | 0.868\* |
| **LH/FSH ratio** | 1.33 (0.93-1.77) | 0.82 (0.28-NR) | 0.087\* |
| **TSH (mUl/ml)** | 1.75 (1.33-2.79) | 1.27 (0.97-NR) | 0.066\* |
| **E2 (pg/ml)** | 53.9 (31.8-72.9) | 51.8 (51.8-51.8) | 0.844\* |
| **Androstenedione (ng/ml)** | 1.5 ± 0.61 | 1.7 ± 0.13 | 0.567\* |
| **DHEAS (ug/dL)** | 151.02 ± 64.12 | 203 (186-NR) | 0.066\*\* |
| **Free testosterone (pg/ml)** | 1.47 (0.91-2.47) | 1 (0.98-NR) | 0.317\* |
| **Fasting insulin (uUl/ml)** | 4.68 (2.63-9.16) | 5.62 (2-NR) | 0.920\* |
| **Post meal insulin (uUl/ml)** | 27.6 (13.3-40.9) | 46.5 (38.4-NR) | 0.067\* |
| **Fasting blood glucose (mg/dL)** | 83.73 ± 8.83 | 85.33 ± 2.52 | 0.758\*\* |
| **Post meal glucose (mg/dL)** | 80.5 (70.65-95) | 76 (73-NR) | 0.867\* |
| **HOMA-IR** | 0.9 (0.54-2.07) | 1.22 (0.42-NR) | 0.90\* |
| **HOMA-IS** | 0.5 (0.022-0.082) | 0.04 (0.021-NR) | 0.90\* |
| **Glycosylated hemoglobin (%)** | 5.27 (5.05-5.75) | 5.25 (4.87-NR) | 0.934\* |
| **Total ovarian volume (cm3)** | 12.3 (9.83-19.16) | 9.4 (7.53-NR) | 0.209\* |
| **Total AFC (number of follicles)** | 27 (23-35) | 31 (17-NR) | 0.961\* |

BMI: Body mass index; FSH: Follicle stimulating hormone; AMH: Anti-Müllerian hormone; LH: Luteinizing hormone; TSH: Thyroid-Stimulating hormone; E2: Estradiol; DHEAS: Dehydroepiandrosterone sulfate; HOMA-IR: Homeostasis model assessment-Insulin resistance; HOMA-IS: Homeostasis model assessment-Insulin sensitive; AFC: Antral follicular count; NR: No report.

\*Mann-Whitney U-test (no-continuous variables). Data are expressed as median (interquartile range).

\*\* Student's t-test (continuous variables). Data are expressed as mean ± standard deviation.

**Supplementary Table 5. Clinical and endocrine-metabolic parameters of women with PCOS according to the genotypes of rs2272046 in *HMGA2* gene.**

|  |  |  |  |
| --- | --- | --- | --- |
| rs2272046 | | | |
|  | **AA** | **AC** | **P-value** |
| **Case number** | 46 | 3 |  |
| **Age (years)** | 27.5 (23-32) | 37 (30-NR) | **0.039\*** |
| **Weight (kg)** | 60 (55-72.25) | 87 (56-NR) | 0.162\* |
| **Height (m)** | 1.62 ± 0.07 | 1.62 ± 0.04 | 0.895\* |
| **BMI (kg/m2)** | 23.16 (21.45-25.36) | 32.75 (22.43-NR) | 0.144\* |
| **Menarche (years)** | 13 (12-14) | 13 (11-NR) | 0.429\* |
| **Menstrual cycle (days)** | 31 (30-45) | 28 (28-NR) | 0.398\* |
| **Menstrual cycle length (days)** | 5 (4-8) | 5(5-NR) | 0.330\* |
| **FSH (mUl/ml)** | 5.81 (2.57-8.83) | 4.9 (3.94-NR) | 0.707\* |
| **AMH (ng/ml)** | 8.2 (5.07-12.78) | 7.77 (5.03-NR) | 0.588\* |
| **LH (mUl/ml)** | 6.87 (4.58-10.25) | 5.42 (3-NR) | 0.770\* |
| **LH/FSH ratio** | 1.33 (0.86-1.77) | 1.03 (0.76-NR) | 0.182\* |
| **TSH (mUl/ml)** | 1.65 (1.29-2.66) | 2.49 (2.49-NR) | 0.061\* |
| **E2 (pg/ml)** | 52.1 (30.7-71.1) | 80.7 (71.6-NR) | 0.081\* |
| **Androstenedione (ng/ml)** | 1.51 ± 0.56 | 1.51 ± 1.25 | 0.993\*\* |
| **DHEAS (ug/dL)** | 159.11 ± 61.99 | 85.3 ± 62.4 | 0.052\*\* |
| **Free testosterone (pg/ml)** | 1.36 (0.91-2.47) | 1.29 (0.72-NR) | 0.770\* |
| **Fasting insulin (uUl/ml)** | 4.64 (2.4-8.9) | 9.21 (8.46-NR) | 0.249\* |
| **Post meal insulin (uUl/ml)** | 28.55 (13.33-42.93) | 32.35 (19.6-NR) | 0.768\* |
| **Fasting blood glucose (mg/dL)** | 83.36 ± 8.45 | 91 ± 8.66 | 0.137\*\* |
| **Post meal glucose (mg/dL)** | 80 (70.65-95) | 88 (84-NR) | 0.196\* |
| **HOMA-IR** | 0.85 (0.53-2.04) | 2.03 (1.69-NR) | 0.193\* |
| **HOMA-IS** | 0.052 (0.02-0.08) | 0.02 (0.02-NR) | 0.193\* |
| **Glycosylated hemoglobin (%)** | 5.24 (5.01-5.75) | 5.5 (5.06-NR) | 0.617\* |
| **Total ovarian volume (cm3)** | 12.19 (9.5-17.36) | 22.72 (19.3-NR) | **0.027\*** |
| **Total AFC (number of follicles)** | 27.5 (23.25-34.75) | 30 (23-NR) | 0.813\* |

BMI: Body mass index; FSH: Follicle stimulating hormone; AMH: Anti-Müllerian hormone; LH: Luteinizing hormone; TSH: Thyroid-Stimulating hormone; E2: Estradiol; DHEAS: Dehydroepiandrosterone sulfate; HOMA-IR: Homeostasis model assessment-Insulin resistance; HOMA-IS: Homeostasis model assessment-Insulin sensitive; AFC: Antral follicular count; NR: No report.

\*Mann-Whitney U-test (no-continuous variables). Data are expressed as median (interquartile range).

\*\* Student's t-test (continuous variables). Data are expressed as mean ± standard deviation.

**Supplementary Table 6. Clinical and endocrine-metabolic parameters of women with PCOS according to the recessive model of rs2292239 in *ERBBB3* gene.**

|  |  |  |
| --- | --- | --- |
| rs2292239 | | |
|  | **GG+GT** | **TT** |
| **Case number** | 48 | 1 |
| **Age (years)** | 28 (24-32.75) | 23 |
| **Weight (kg)** | 60 (55-72.75) | 80 |
| **Height (m)** | 1.62 ± 0.06 | 1.58 |
| **BMI (kg/m2)** | 23.16 (21.48-25.38) | 32.05 |
| **Menarche (years)** | 13 (12-14) | 9 |
| **Menstrual cycle (days)** | 31 (30-45) | 25 |
| **Menstrual cycle length (days)** | 5 (4-8) | 3 |
| **FSH (mUl/ml)** | 5.59 (2.61-8.8) | 10.1 |
| **AMH (ng/ml)** | 8.13 (5.05-12.58) | 6.16 |
| **LH (mUl/ml)** | 6.75 (4.53-10.35) | 9.7 |
| **LH/FSH ratio** | 1.31 (0.85-1.76) | 0.96 |
| **TSH (mUl/ml)** | 1.71 (1.29-2.72) | 1.63 |
| **E2 (pg/ml)** | 52.7 (31.8-72.9) | 65.9 |
| **Androstenedione (ng/ml)** | 1.50 ± 0.60 | 1.86 |
| **DHEAS (ug/dL)** | 155.44 ± 64.31 | 114 |
| **Free testosterone (pg/ml)** | 1.34 (0.91-2.37) | 3.83 |
| **Fasting insulin (uUl/ml)** | 4.68 (2.48-9.65) | 8.9 |
| **Post meal insulin (uUl/ml)** | 28.8 (13.35-44.35) | 19.9 |
| **Fasting blood glucose (mg/dL)** | 83.64 ± 8.56 | 93 |
| **Post meal glucose (mg/dL)** | 80.5 (71.5-95) | 78 |
| **HOMA-IR** | 0.9 (0.54-2.0) | 2.04 |
| **HOMA-IS** | 0.05 (0.02-0.08) | 0.022 |
| **Glycosylated hemoglobin (%)** | 5.28 (5.07-5.76) | 4.7 |
| **Total ovarian volume (cm3)** | 12.2 (9.6-19.01) | 16.4 |
| **Total AFC (number of follicles)** | 28 (23-35) | 27 |

BMI: Body mass index; FSH: Follicle stimulating hormone; AMH: Anti-Müllerian hormone; LH: Luteinizing hormone; TSH: Thyroid-Stimulating hormone; E2: Estradiol; DHEAS: Dehydroepiandrosterone sulfate; HOMA-IR: Homeostasis model assessment-Insulin resistance; HOMA-IS: Homeostasis model assessment-Insulin sensitive; AFC: Antral follicular count.

**Supplementary Table 7. MassArray design details for SNPs (rs2059807 in *INSR*, rs4784165 in *TOX3*, rs1894116 in *YAP1*, rs2272046 in *HMGA2*, and rs2292239 in *ERBB3*).**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **TERM** | **SNP\_ID** | **2nd-PCRP** | **1st-PCRP** | **AMP\_LEN** | **UP\_CONF** | **MP\_CONF** | **Tm (NN)** | **PcGC** | **PWARN** | **UEP\_DIR** | **UEP\_MASS** | **UEP\_SEQ** | **EXT1\_CALL** | **EXT1\_MASS** | **EXT1\_SEQ** | **EXT2\_CALL** | **EXT2\_MASS** | **EXT2\_SEQ** |
| iPLEX | rs2059807 | ACGTTGGATGATGTGAATCAGACCTCTTGC | ACGTTGGATGAGCCAATAACCATATCAAGG | 98 | 93.0 | 72.3 | 48.0 | 33.3 |  | R | 6355.2 | AATCAGACCTCTTGCTTTTAA | G | 6602.3 | AATCAGACCTCTTGCTTTTAAC | A | 6682.3 | AATCAGACCTCTTGCTTTTAAT |
| iPLEX | rs2272046 | ACGTTGGATGGGATTCAGTAATTGGCCTTG | ACGTTGGATGACATTCTGCATGCATTGTCC | 109 | 96.8 | 72.3 | 50.4 | 52.9 |  | F | 6533.2 | ggagTGGCCTTGGGACATTTG | C | 6780.4 | ggagTGGCCTTGGGACATTTGC | A | 6804.4 | ggagTGGCCTTGGGACATTTGA |
| iPLEX | rs2292239 | ACGTTGGATGGCTATCACCCTTACTTCTGC | ACGTTGGATGACCCTAGATCCCTTAAGTGC | 106 | 99.9 | 72.3 | 45.5 | 33.3 |  | F | 7761.1 | gggcGTGAAGAGACTTTTGAATCTA | G | 8048.3 | gggcGTGAAGAGACTTTTGAATCTAG | T | 8088.2 | gggcGTGAAGAGACTTTTGAATCTAT |
| iPLEX | rs1894116 | ACGTTGGATGAAATTTAGTTGCATTGAGG | ACGTTGGATGAAGGATTGACCACTGTCAAG | 113 | 77.8 | 72.3 | 46.7 | 22.2 |  | R | 8231.4 | TCTACATAATATTGATTCTAGACAATT | G | 8478.6 | TCTACATAATATTGATTCTAGACAATTC | A | 8558.5 | TCTACATAATATTGATTCTAGACAATTT |
| iPLEX | rs4784165 | ACGTTGGATGGAGCCAGCCGTACATTAATC | ACGTTGGATGGGAATTTAAGTTATTTTCCC | 115 | 78.6 | 72.3 | 49.3 | 28.6 | D | R | 8612.7 | GTCACATAATAACTTGAAAAACTATGAG | G | 8859.8 | GTCACATAATAACTTGAAAAACTATGAGC | T | 8883.9 | GTCACATAATAACTTGAAAAACTATGAGA |

TERM: Termination chemistry; SNP\_ID: Reference of the sequence; 2nd-PCRP: First Forward Sequence; 1st-PCRP: First Reverse Sequence; AMP\_LEN: Length of the amplicon; UP\_CONF: Uniplex Amplification Score (this score indicates how well the amplicon meets the design criteria, individually); MP\_CONF: multiplex amplification score (this score indicates how well the amplicon meets the design criteria, taking into account the other primers included in the multiplex reaction); Tm (NN): Melting temperature for the extension primer; PcGC: Percentage of GC contained in the first extension; UEP\_DIR: Address of the extension first; UEP\_MASS: Mass of the first extension; UEP\_SEQ: Sequence of extension first; EXT1\_CALL: First allelic variant; EXT1\_MASS: Mass of the sequence of the first extension + genotype of the first allelic variant; EXT1\_SEQ: Extension primer sequence + first allelic variant; EXT2\_CALL: Second allelic variant; EXT2\_MASS: Mass of the sequence of the first extension + g; EXT2\_SEQ: Extension primer sequence + second allelic variant