

Table S1: Detail patients' characteristics

| Patient | gender | age | USP8 mutation (0/1) | USP48 mutation (0/1) | Functional status | cortisol 08.00 (ug/dl) - 6.2-19.4 ug/dl | ACTH 08.00 (pg/dl) (10-60 pg/ml) | UFC (4.3-176 ug/24h) | cortisol 24.00 - single sleeping midnight serum cortisol level (<1.8ug/dl) | late night salivary cortisol (ug/dl, <9.21 ug/dl) | Preoperative treatment | Knosp grade | micro vs. MAKRAdenoma | tumor size (mm) | ACTH (IHC) | GH (IHC) | TSH (IHC) | FSH (IHC) | LH (IHC) | o-subunit (IHC) | Ki-67 (IHC) | Patomorfolological diagnosis             | tumor tissue content in the sample (%) |
|---------|--------|-----|---------------------|----------------------|-------------------|---|----------------------------------|----------------------|--|---|------------------------|-------------|-----------------------|-----------------|------------|----------|-----------|-----------|----------|-----------------|-------------|--|--|
| C1      | f      | 50  | 0                   | 0                    | Cushing's disease | 29.1                                    | 39.4                             | 439                  | 19.8   | na  | none                   | 4           | M                     | 21x16x20        | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | densly granulated corticotroph adenoma   | 97                                     |
| C2      | f      | 66  | 0                   | 0                    | Cushing's disease | 25.64                                   | 61                               | 713                  | 21.2   | na  | none                   | 4           | M                     | 26x14x15        | 1          | 0        | 0         | 0         | 0        | 0               | >5%         | sparsely granulated corticotroph adenoma | 98                                     |
| C3      | m      | 42  | 0                   | 0                    | Cushing's disease | 23.6                                    | 82.3                             | 626.58               | 21.4   | na  | unknown                | 2           | M                     | 15x12x14        | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | densly granulated corticotroph adenoma   | 97                                     |
| C4      | f      | 37  | 0                   | 0                    | Cushing's disease | 16.6                                    | 36.9                             | 639                  | 15.9   | na  | none                   | 2           | m                     | 7x10x10         | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | densly granulated corticotroph adenoma   | 99                                     |
| C5      | f      | 24  | 0                   | 0                    | Cushing's disease | 17.46                                   | 65.9                             | 520                  | 12.9   | na  | none                   | 1           | M                     | 20x20x20        | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | sparsely granulated corticotroph adenoma | 98                                     |
| C6      | f      | 40  | 0                   | 0                    | Cushing's disease | 26.4                                    | 90                               | 497                  | 19.4   | na  | none                   | 1           | M                     | 26x18x20        | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | densly granulated corticotroph adenoma   | 96                                     |
| C7      | f      | 61  | 0                   | 0                    | Cushing's disease | 38.6                                    | 112                              | 739                  | 29.1   | na  | none                   | 4           | M                     | 25x32x15        | 1          | 0        | 0         | 0         | 0        | 1               | <3%         | sparsely granulated corticotroph adenoma | 98                                     |
| C8      | m      | 31  | 1                   | 0                    | Cushing's disease | 31.4                                    | 79.5                             | 810                  | 34.4   | na  | unknown                | 2           | M                     | 26x20x18        | 1          | 0        | 0         | 0         | 0        | 1               | 3%          | sparsely granulated corticotroph adenoma | 99                                     |
| C9      | f      | 48  | 0                   | 0                    | Cushing's disease | 16.4                                    | 37                               | 215                  | 17.8   | na  | unknown                | 1           | m                     | 7x5x6           | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | densly granulated corticotroph adenoma   | 96                                     |
| C10     | f      | 28  | 1                   | 0                    | Cushing's disease | 49.7                                    | 39                               | 490                  | 36.5   | na  | none                   | 4           | M                     | 14x10x10        | 1          | 0        | 0         | 0         | 0        | 0               | >5%         | densly granulated corticotroph adenoma   | 99                                     |
| C11     | f      | 67  | 1                   | 0                    | Cushing's disease | 31                                      | 102                              | 550                  | 16.32  | na  | unknown                | 3           | M                     | 27 x 20 x 25    | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | sparsely granulated corticotroph adenoma | 95                                     |
| C12     | f      | 33  | 0                   | 1                    | Cushing's disease | 21.4                                    | 49                               | 547                  | 11.9   | 0.41  | none                   | 1           | M                     | 11x11x15        | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | densly granulated corticotroph adenoma   | 90                                     |
| C13     | f      | 42  | 1                   | 0                    | Cushing's disease | 31.4                                    | 37.3                             | 498                  | 18   | na  | none                   | 1           | M                     | 8x11x12         | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | densly granulated corticotroph adenoma   | 99                                     |
| C14     | f      | 76  | 0                   | 0                    | Cushing's disease | 23.6                                    | 89                               | 298                  | 21.9   | na  | none                   | 3           | M                     | 27x22x17        | 1          | 0        | 0         | 0         | 0        | 0               | >5%         | sparsely granulated corticotroph adenoma | 99                                     |
| C15     | f      | 59  | 1                   | 0                    | Cushing's disease | 26.3                                    | 86.9                             | 530                  | 24.2   | na  | none                   | 1           | m                     | 5x4x5           | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | sparsely granulated corticotroph adenoma | 100                                    |
| C16     | f      | 51  | 0                   | 0                    | Cushing's disease | 31.9                                    | 107                              | 610                  | 23.5   | na  | none                   | 0           | m                     | 5x5x5           | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | sparsely granulated corticotroph adenoma | 97                                     |
| C17     | f      | 43  | 0                   | 1                    | Cushing's disease | 23.7                                    | 39.1                             | 448                  | 19   | na  | none                   | 0           | m                     | 4x4x4           | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | densly granulated corticotroph adenoma   | 99                                     |
| C18     | f      | 58  | 0                   | 0                    | Cushing's disease | 11.9                                    | 87                               | 348                  | 14.7   | 0.28  | none                   | 2           | M                     | 20x15x26        | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | densly granulated corticotroph adenoma   | 99                                     |
| C19     | f      | 23  | 1                   | 0                    | Cushing's disease | 21.8                                    | 48.2                             | 719                  | 23.4   | na  | none                   | 0           | M                     | 11x9x9          | 1          | 0        | 0         | 0         | 0        | 0               | >10%        | densly granulated corticotroph adenoma   | 99                                     |
| C20     | f      | 36  | 1                   | 0                    | Cushing's disease | 39.2                                    | 63.1                             | 387                  | 11.6   | na  | none                   | 1           | m                     | 7x7x7           | 1          | 0        | 0         | 0         | 0        | 0               | >3%         | densly granulated corticotroph adenoma   | 99                                     |
| C21     | f      | 31  | 0                   | 0                    | Cushing's disease | 33.4                                    | 39.6                             | 299                  | 26.5   | na  | none                   | 1           | M                     | 14x16x15        | 1          | 0        | 0         | 0         | 0        | 1               | <1%         | densly granulated corticotroph adenoma   | 99                                     |
| C22     | f      | 30  | 0                   | 0                    | Cushing's disease | 28.4                                    | 43.2                             | 510                  | 19.8   | na  | none                   | 1           | m                     | 7x7x7           | 1          | 0        | 0         | 0         | 0        | 0               | >3%         | densly granulated corticotroph adenoma   | 99                                     |
| C23     | f      | 35  | 1                   | 0                    | Cushing's disease | 21                                      | 48.3                             | 406                  | 24.1   | 0.29  | none                   | 1           | M                     | 12x11x11        | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | densly granulated corticotroph adenoma   | 97                                     |
| C24     | f      | 52  | 1                   | 0                    | Cushing's disease | 26.3                                    | 42.7                             | 390                  | 19.3   | na  | none                   | 1           | m                     | 6x6x7           | 1          | 0        | 0         | 0         | 0        | 1               | <3%         | densly granulated corticotroph adenoma   | 98                                     |
| C25     | f      | 34  | 1                   | 0                    | Cushing's disease | 21.6                                    | 39.3                             | 276                  | 23.8   | na  | none                   | 0           | m                     | 4x4x4           | 1          | 0        | 0         | 0         | 0        | 1               | <1%         | densly granulated corticotroph adenoma   | 80                                     |
| C26     | m      | 71  | 0                   | 0                    | Cushing's disease | 36.2                                    | 129                              | 298                  | 21.1   | na  | none                   | 9           | M                     | 21x20x16        | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | sparsely granulated corticotroph adenoma | 100                                    |
| C27     | f      | 67  | 1                   | 0                    | Cushing's disease | 21.9                                    | 43.1                             | 319                  | 13.9   | na  | none                   | 3           | m                     | 3x4x9           | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | densly granulated corticotroph adenoma   | 100                                    |
| C28     | f      | 41  | 0                   | 0                    | Cushing's disease | 27.1                                    | 93.6                             | 284                  | 15.3   | na  | unknown                | 1           | m                     | 7x6x5           | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | densly granulated corticotroph adenoma   | 98                                     |
| S1      | m      | 57  | 0                   | 0                    | Silent            | 11.4                                    | 74.9                             | 117                  | 0.8  | 0.01; 0.01  | none                   | 3           | M                     | 24x33x28        | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | sparsely granulated corticotroph adenoma | 95                                     |
| S2      | m      | 54  | 0                   | 0                    | Silent            | 11.3                                    | 57.3                             | 27.3                 | 0.8  | 0.01;0.009  | none                   | 2           | M                     | 26x19x21        | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | sparsely granulated corticotroph adenoma | 100                                    |
| S3      | m      | 53  | 0                   | 0                    | Silent            | 21.4                                    | 51.3                             | 108                  | 1.1  | 0.01;0.01   | none                   | 4           | M                     | 28x24x19        | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | densly granulated corticotroph adenoma   | 99                                     |
| S4      | m      | 55  | 0                   | 0                    | Silent            | 27.1                                    | 29.1                             | 39.8                 | 0.3  | na  | none                   | 1           | M                     | 12x12x15        | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | sparsely granulated corticotroph adenoma | 90                                     |
| S5      | m      | 77  | 0                   | 0                    | Silent            | 19.7                                    | 62.3                             | 47.2                 | 1.7  | 0.03;0.03   | none                   | 1           | M                     | 21x19x13        | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | densly granulated corticotroph adenoma   | 95                                     |
| S6      | f      | 54  | 1                   | 0                    | Silent            | 9.1                                     | 47.5                             | 124                  | 1.9  | na  | none                   | 2           | M                     | 25x28x21        | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | densly granulated corticotroph adenoma   | 99                                     |
| S7      | m      | 45  | 0                   | 0                    | Silent            | 12.1                                    | 32.1                             | 110                  | 0.9  | na  | none                   | 1           | M                     | 34x25x20        | 1          | 0        | 0         | 0         | 0        | 0               | 3%          | sparsely granulated corticotroph adenoma | 99                                     |
| S8      | f      | 64  | 0                   | 0                    | Silent            | 19.2                                    | 46.7                             | 29.8                 | 0.9  | na  | none                   | 2           | M                     | 25x18x15        | 1          | 0        | 0         | 0         | 0        | 1               | >5%         | densly granulated corticotroph adenoma   | 100                                    |
| S9      | m      | 44  | 0                   | 0                    | Silent            | 21.3                                    | 57.0                             | 136                  | 1.1  | 0.03;0.02   | none                   | 1           | M                     | 20x25x32        | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | densly granulated corticotroph adenoma   | 90                                     |
| S10     | f      | 43  | 0                   | 0                    | Silent            | 7.8                                     | 39.7                             | 13.7                 | 0.4  | 0.02;0.05   | none                   | 1           | M                     | 21x14x21        | 1          | 0        | 0         | 0         | 0        | 0               | >3%         | sparsely granulated corticotroph adenoma | 90                                     |
| S11     | f      | 34  | 0                   | 0                    | Silent            | 19.7                                    | 63.9                             | 63.84                | 0.8  | na  | none                   | 0           | M                     | 21x22x15        | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | densly granulated corticotroph adenoma   | 99                                     |
| S12     | f      | 42  | 0                   | 0                    | Silent            | 12.9                                    | 36.7                             | 111.7                | 1.9  | 0.03;0.02   | none                   | 2           | M                     | 17x25x31        | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | sparsely granulated corticotroph adenoma | 98                                     |
| S13     | f      | 23  | 1                   | 0                    | Silent            | 19.9                                    | 42.1                             | 139                  | 1.3  | 0.06;0.03   | none                   | 0           | M                     | 19x15x13        | 1          | 0        | 0         | 0         | 0        | 0               | >10%        | sparsely granulated corticotroph adenoma | 99                                     |
| S14     | f      | 61  | 0                   | 0                    | Silent            | 20.1                                    | 61.2                             | 97.4                 | 0.4  | 0.09;0.02   | none                   | 1           | M                     | 15x12x14        | 1          | 0        | 0         | 0         | 0        | 1               | <3%         | sparsely granulated corticotroph adenoma | 99                                     |
| S15     | m      | 54  | 0                   | 0                    | Silent            | 17.1                                    | 51.3                             | 59.8                 | 0.4  | na  | none                   | 2           | M                     | 21x18x17        | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | densly granulated corticotroph adenoma   | 99                                     |
| S16     | f      | 69  | 0                   | 0                    | Silent            | 29.7                                    | 41.3                             | 37.91                | 0.9  | na  | none                   | 4           | M                     | 19x25x28        | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | sparsely granulated corticotroph adenoma | 98                                     |
| S17     | f      | 60  | 0                   | 0                    | Silent            | 6.8                                     | 14.7                             | 123                  | 1.4  | na  | none                   | 3           | M                     | 24 x18x20       | 1          | 0        | 0         | 0         | 0        | 0               | 3%          | sparsely granulated corticotroph adenoma | 98                                     |
| S18     | m      | 61  | 0                   | 0                    | Silent            | 10.9                                    | 21.8                             | 68.8                 | 4.9  | na  | none                   | 1           | M                     | 20x14x15        | 1          | 0        | 0         | 0         | 0        | 0               | <3%         | sparsely granulated corticotroph adenoma | 99                                     |
| S19     | f      | 29  | 1                   | 0                    | Silent            | 50.8                                    | 61.3                             | 94.76                | 0.4  | 0.02;0.04   | none                   | 1           | M                     | 17x12x18        | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | densly granulated corticotroph adenoma   | 100                                    |
| S20     | f      | 77  | 1                   | 0                    | Silent            | 13.6                                    | 47.9                             | 124                  | 1.4  | na  | none                   | 1           | M                     | 12x15x10        | 1          | 0        | 0         | 0         | 0        | 0               | <1%         | sparsely granulated corticotroph adenoma | 98                                     |

**Table S2: Gene set over-representation analysis (GSOA); Top 20 pathways enriched for the genes that are targets of differentially expressed miRNAs**

## GO molecular function

|    | GO molecular function term   | fold Enrich | p-value  | adjusted p-value |
|----|--|-------------|----------|------------------|
| 1  | steroid hormone receptor activity (GO:0003707)   | 7.86        | 1.87E-04 | 1.75E-02         |
| 2  | nuclear receptor activity (GO:0004879)   | 5.2         | 9.24E-07 | 1.42E-04         |
| 3  | ligand-activated transcription factor activity (GO:0098531)                                  | 5.2         | 9.24E-07 | 1.34E-04         |
| 4  | regulatory RNA binding (GO:0061980)  | 5.06        | 2.95E-04 | 2.66E-02         |
| 5  | transcription coregulator binding (GO:0001221)   | 3.6         | 1.31E-04 | 1.27E-02         |
| 6  | phosphatase binding (GO:0019902)   | 3.09        | 7.99E-05 | 8.03E-03         |
| 7  | DNA-binding transcription repressor activity, RNA polymerase II-specific (GO:0001222)        | 3.09        | 1.98E-05 | 2.25E-03         |
| 8  | DNA-binding transcription repressor activity (GO:0001217)                                    | 2.98        | 3.11E-05 | 3.39E-03         |
| 9  | DNA-binding transcription activator activity (GO:0001216)                                    | 2.5         | 6.56E-07 | 1.07E-04         |
| 10 | DNA-binding transcription activator activity, RNA polymerase II-specific (GO:0001228)        | 2.47        | 1.12E-06 | 1.55E-04         |
| 11 | RNA polymerase II cis-regulatory region sequence-specific DNA binding (GO:0000978)           | 2.27        | 2.37E-09 | 3.10E-06         |
| 12 | cis-regulatory region sequence-specific DNA binding (GO:0000987)                             | 2.27        | 1.72E-09 | 4.50E-06         |
| 13 | RNA polymerase II-specific DNA-binding transcription factor binding (GO:0061629)             | 2.25        | 3.92E-04 | 3.41E-02         |
| 14 | DNA-binding transcription factor activity (GO:0003700)                                       | 2.22        | 4.25E-09 | 2.78E-06         |
| 15 | DNA-binding transcription factor activity, RNA polymerase II-specific (GO:0000981)           | 2.2         | 1.03E-08 | 4.48E-06         |
| 16 | RNA polymerase II transcription regulatory region sequence-specific DNA binding (GO:0000979) | 2.2         | 5.63E-09 | 2.95E-06         |
| 17 | transcription factor binding (GO:0008134)  | 2.13        | 2.50E-06 | 3.27E-04         |
| 18 | transcription cis-regulatory region binding (GO:0000976)                                     | 2.09        | 1.27E-08 | 4.74E-06         |
| 19 | transcription regulatory region nucleic acid binding (GO:0001067)                            | 2.08        | 1.34E-08 | 4.38E-06         |
| 20 | sequence-specific double-stranded DNA binding (GO:1990837)                                   | 2.01        | 4.28E-08 | 1.02E-05         |

## GO biological process

|   | GO biological process term                                    | fold Enrich | p-value  | adjusted p-value |
|---|---|-------------|----------|------------------|
| 1 | negative regulation of stem cell differentiation (GO:2000737) | 8.24        | 4.64E-04 | 2.40E-02         |
| 2 | neuronal stem cell population maintenance (GO:0097150)        | 7.21        | 2.77E-04 | 1.67E-02         |
| 3 | response to muscle stretch (GO:0035994)                       | 5.77        | 7.72E-04 | 3.54E-02         |
| 4 | maintenance of cell number (GO:0098727)                       | 4.72        | 6.49E-08 | 1.49E-05         |
| 5 | steroid hormone mediated signaling pathway (GO:0043401)       | 4.63        | 5.65E-05 | 4.45E-03         |

|    |  |      |          |          |
|----|--|------|----------|----------|
| 6  | stem cell population maintenance (GO:0019827)                                    | 4.52 | 4.96E-07 | 7.41E-05 |
| 7  | hormone-mediated signaling pathway (GO:0009755)                                  | 4.47 | 2.29E-06 | 2.71E-04 |
| 8  | somatic stem cell population maintenance (GO:0035019)                            | 4.45 | 6.28E-04 | 3.01E-02 |
| 9  | negative regulation of fat cell differentiation (GO:0045599)                     | 4.28 | 7.92E-04 | 3.59E-02 |
| 10 | neural crest cell development (GO:0014032)                                       | 4.25 | 2.18E-04 | 1.37E-02 |
| 11 | lung morphogenesis (GO:0060425)  | 4.12 | 9.88E-04 | 4.27E-02 |
| 12 | associative learning (GO:0008306)  | 4.12 | 5.17E-04 | 2.56E-02 |
| 13 | neural crest cell differentiation (GO:0014033)                                   | 4.01 | 1.76E-04 | 1.19E-02 |
| 14 | mesenchymal cell development (GO:0014031)  | 4    | 3.36E-04 | 1.89E-02 |
| 15 | stem cell development (GO:0048864)   | 3.88 | 4.13E-04 | 2.25E-02 |
| 16 | regulation of Rho protein signal transduction (GO:0035023)                       | 3.86 | 7.86E-04 | 3.57E-02 |
| 17 | intracellular receptor signaling pathway (GO:0030522)                            | 3.76 | 1.46E-06 | 1.86E-04 |
| 18 | post-embryonic development (GO:0009791)  | 3.74 | 9.59E-04 | 4.18E-02 |
| 19 | response to estrogen (GO:0043627)  | 3.74 | 9.59E-04 | 4.17E-02 |
| 20 | positive regulation of pri-miRNA transcription by RNA polymerase II (GO:1902895) | 3.67 | 6.12E-04 | 2.95E-02 |

**Table S3: Sequences of qRT-PCR primers**

|                                      |                      |                          |
|--------------------------------------|----------------------|--------------------------|
| primers for human cDNA amplification |                      |                          |
| <b>POMC</b>                          | AGGACCTCACCACGGAAAG  | GGGAACATGGGAGTCTCGG      |
| <b>NR3C1</b>                         | TGCTCCTTCTGCGTTCACAA | CCATCAGTGAATATCAACTCTGGC |
| <b>NR3C2</b>                         | GGGGATGAGGCTTCAGGATG | AGTTGTGTTGCCCTTCCACT     |
| <b>GAPDH</b>                         | GAAGATGGTGATGGGATTTC | GAGGTGAAGGTCGGAGTC       |

|                                      |                         |                         |
|--------------------------------------|-------------------------|-------------------------|
| primers for mouse cDNA amplification |                         |                         |
| <b>NR3C1</b>                         | TGGAGAGGACAACCTGACTTCC  | ACGGAGGAGAACTCACATCTGG  |
| <b>NR3C2</b>                         | AACCACACGGTGACCTGTCATC  | AGTGACACCCAGAAGCCTCATC  |
| <b>GAPDH</b>                         | CATCACTGCCACCCAGAAGACTG | ATGCCAGTGAGCTTCCCGTTCAG |