Supplemental Information

Loss of microRNA-7a2 induces hypogonadotropic hypogonadism and infertility

Kashan Ahmed et al.
**Supplemental Figure 1.** Generation of mir-7b KO and phenotypic characterization. The generation of mir-7a1 KO and mir-7a2 KO was described previously (21). (A) Strategy used to generate mir-7b KO mice by homologous recombination. miRNA sequences were flanked with loxP sites and recombination induced by breeding mice with DeleterCre transgenics. Bgl1 digested DNA and southern blotting using the indicated miR-7b Probe was used to identify targeted clones. Wildtype allele: 13.0 kb; Mutant allele: 7.4 kb. (B) Southern blotting of genomic DNA from wild type (+/+), heterozygotes (+/–) and homozygotes (–/–) mir-7b mutant mice. DNA was digested with BglI and blotting performed with probe A. M, Molecular weight marker. (C and D) Relative miR-7a (C) and miR-7b (D) Expression in pituitary glands of controls (+/+) and mir-7b KO (–/–) mice (n = 4). (E and F) Body weights (E) and length (F) of male mir-7a1 KO, mir-7a2 KO or respective control mice (mir-7a1 control, mir-7a2 control n = 11; mir-7a1 KO, mir-7a2 KO, n = 7). Body length measured as distance from nose to base of tail. (G) Histological testes sections stained with hematoxylin-eosin of control (left image) or mir-7a2 KO mice (right image). Arrows indicate: 1: Leydig cells, 2: Basement membrane, 3. Spermatogonia, 4: Spermatids, 5: Spermatozoa, 6: Spermatozoa tails, 7: Sertoli cell. Shown are representative images of three mice per genotype, scale bar, 100 µm. (H) Gonadal fat pad weights normalized to body weight of 16 week-old male control or mir-7a2 KO mice (mir-7a2 control n = 20; mir-7a2 KO, n = 5). (I and J) Body weights (I) and length (J) of female mir-7a1 KO, mir-7a2 KO or respective control mice (mir-7a1 control, mir-7a1 KO, n = 4; mir-7a2 control, n = 21; mir-7a2 KO, n = 7). The measurements were performed at 2 months of age. (K) Gonadal fat pad weights normalized to body weight of 16 week-old female control or mir-7a2 KO mice (mir-7a2 control, n = 21; mir-7a2 KO, n = 7). (L and M) Magnetic resonance imaging analysis revealing fat mass (L) and lean mass (M) in 16 week-old control or mir-7a2 KO female mice (mir-7a2 control n = 6; mir-7a2 KO, n = 5). All data are mean ± SD. *** P < 0.001 by t-test.
Supplemental Figure 2. (A and B) Absolute expression levels of miR-7a or miR-7b in indicated organs of male (A) and female (B) wildtype mice (n = 4). (C and D) Relative expression levels of miR-7a (C) or miR-7b (D) in pituitary of male control or mir-7a2 KO mice (mir-7a2 control, mir-7a2 KO, n = 3). (E and F) Relative expression levels of miR-7a (E) or miR-7b (F) in pituitary of male control or mir-7a1 KO mice (mir-7a1 control, mir-7a1 KO, n = 4). All data are mean ± SD. *** P < 0.001 by t-test.
Supplemental Figure 3. (A) Relative mRNA levels in pituitaries of 14 day old mice measured by qPCR (mir-7a2 control, n = 4; mir-7a2 KO, n = 3). (B and C) Plasma LH (B) and FSH (C) levels of miR-7a2 KO (7a2–/–) and littermate control mice (7a2+/+) that were injected with Buserelin of PBS 15 min prior to blood collection (n = 6 for each group). (D and E) Relative expression levels of genes encoding pituitary releasing hormones in hypothalamus of male (D) and female (E) mir-7a2 KO or control mice (males, mir-7a2 control, mir-7a2 KO, n = 3, females, mir-7a2 control, mir-7a2 KO, n = 5). (F) Representative immunohistological images of hypothalamic sections stained for GnRH of control (left images) or mir-7a2 KO mice (right images), (WT, mir-7a2 KO, n = 2); scale bar, 100 um. (G and H) Relative expression levels of hypothalamic genes involved in GnRH-neuronal functions in male (G) and female (H) control or mir-7a2 KO mice (male, mir-7a2 control, mir-7a2 KO, n = 3; female, mir-7a2 control, mir-7a2 KO, n = 5). (I) Time elapsed in a food-seeking olfaction test in male and female mir-7a2 KO or control mice (WT, mir-7a2 KO, n = 6). (J and K) Pituitary weight (J) and body weight (K) in male UBC-Cre x mir-7a2flox or Cre-negative mir-7a2flox mice 10 weeks after a 5-day treatment with tamoxifen (TAM) or vehicle (UBC-Cre x mir-7a2flox + vehicle, n = 5; mir-7a2flox + TAM, UBC-Cre x mir-7a2flox + TAM, n = 4. All data are mean ± SD. * P < 0.05; ** P < 0.01; *** P < 0.001 by t-test (A,D,E,G,H) and ANOVA (B,C,I)
Supplemental Figure 4
Ahmed et al.

A

B

C

D

WT1 WT2 WT3 KO1 KO2 KO3

Acvr1
Acvr1b
Acvr1c
Acvr2a
Acvr2b
Egr1
Foxl2
Gnrhr
Smad1
Smad2
Smad3 **
Smad4
Smad5
Smad6
Smad7
Smad8
Smad9

log2

Relative expression

Ad-Ctrl  Ad-miR-7a2

C

D

Ad-Ctrl  Ad-miR-7a2

Relative expression
Supplemental Figure 4. (A) Expression levels of established key factors of early pituitary function. Data from RNA seq of mir-7a2 KO or control mice shown as heat map (n = 3). (B) Expression levels of predicted miR-7 targets in pituitaries of mir-7a2 KO mice that were previously shown to be upregulated in pancreatic islets implicated in insulin granule exocytosis. Data from RNA seq of mir-7a2 KO or control mice shown as heat map (n = 3). (C and D) Relative expression of predicted miR-7 target genes that were more than 1.3-fold upregulated in RNA Seq in gonadotroph cell lines aT3 (C) and LbT2 (D) transduced with adenoviral constructs overexpressing mir7a2 (Ad-mir-7a2) or control (Ad-Ctrl). Fgf1, Kcna1, Prelp, Rgs8, Scnb2, SIC4a4, Snca, and Syt6 were only lowly expressed in aT3 and/or LbT2 cells and could not be analyzed. (aT3, n = 3; LbT2, n = 4). All data are mean ± SD. * P < 0.05; ** P < 0.01; *** P < 0.001 by t-test.
**Supplemental Figure 5.** (A and B) Effect of siRNA-mediated silencing of predicted miR-7 targets that were more than 1.3-fold upregulated in RNA Seq in the gonadotroph cell lines LbT2 (A) or aT3 (B) on mRNA expression of Fshb (A) or Cga (B) 48 h after transfection (n = 3). All data are mean ± SD. * P < 0.05; ** P < 0.01 by t-test.
Supplemental Figure 6. (A and B) Relative expression of gonadotroph hormones Fshb (A) and Lhb (B) in LbT2 cells treated with or without 100 nM dinoprost for 4 h or 8 h (n = 4). (C) Relative expression of gonadotropic hormones Fshb, Lhb and Cga in LbT2 cells overexpressing Grem1 (n = 4). (D and E) Relative expression of Grem1 in LbT2 cells silenced for Glg1 (D) and over-expressing Glg1 (E) (n = 4). All data are mean ± SD. * P < 0.05; ** P < 0.01; *** P < 0.001 by t-test.
## Table 1. Fertility assessment of *mir-7a1*, *mir-7a2* and *mir-7b* KO mice.

<table>
<thead>
<tr>
<th></th>
<th><strong>♀</strong></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th><strong>♂</strong></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic background</td>
<td>7a1</td>
<td>7a2</td>
<td>7a2</td>
<td>7b</td>
<td></td>
<td>7a1</td>
<td>7a2</td>
<td>7a2</td>
<td>7b</td>
</tr>
<tr>
<td>Genotype</td>
<td>–/–</td>
<td>+/–</td>
<td>–/–</td>
<td>–/–</td>
<td></td>
<td>–/–</td>
<td>+/–</td>
<td>–/–</td>
<td>–/–</td>
</tr>
<tr>
<td>Number of animals</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td></td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Pregnancies/mated mouse (%)</td>
<td>81</td>
<td>75</td>
<td>0</td>
<td>78</td>
<td></td>
<td>69</td>
<td>79</td>
<td>0</td>
<td>81</td>
</tr>
<tr>
<td>Average number of progeny/pregnancy</td>
<td>8.3</td>
<td>7.5</td>
<td>0</td>
<td>7.8</td>
<td></td>
<td>9.1</td>
<td>8.9</td>
<td>0</td>
<td>7.8</td>
</tr>
</tbody>
</table>

*Supplementary Table 1*

Ahmed et al.
<table>
<thead>
<tr>
<th>Sequence</th>
<th>Forward (5’-3’)</th>
<th>Reverse (5’-3’)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mir-7b (15.7) kb locus</td>
<td>GCTCCTGTTCATGTTTGA GCGTGGCTCTAGTGCTT GAGTACACTATATTTGCT CTCCGAGTAGGACAAATC</td>
<td>AAATTCTGGGATTGTCTTTTG CTACTTTCCATCTTTACTGT GTGCTCATGTTCCACACCTTG TCTGTAAGCGGATG</td>
</tr>
<tr>
<td>mir-7b Geno PCR1</td>
<td>atccacgttggtgtgctcaggg</td>
<td>ccgtttggtcattcccagaga</td>
</tr>
<tr>
<td>mir-7b Geno PCR2</td>
<td>atccacgttggtgtgctcaggg</td>
<td>gatttgactcngacctcgggtcag</td>
</tr>
<tr>
<td>Gene</td>
<td>Sequence - forward primer</td>
<td>Sequence - reverse primer</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Acsl4</td>
<td>gaaattcacagcatgaatcag</td>
<td>tctacttggaggaacgctcaa</td>
</tr>
<tr>
<td>Arrb1</td>
<td>gcctgacaaagcccagttg</td>
<td>agagcttgcagaaatgtgagc</td>
</tr>
<tr>
<td>Celsr1</td>
<td>gccagtcatgacctttggacta</td>
<td>agctgattcccaatctgcac</td>
</tr>
<tr>
<td>Cga</td>
<td>tccctcaaaagttcagagc</td>
<td>ggaggaatgaagaatatgcagg</td>
</tr>
<tr>
<td>Chd3</td>
<td>actttagtggcgctctgaaag</td>
<td>ggcgtgtctttacctgcgg</td>
</tr>
<tr>
<td>Chd7</td>
<td>cttttcagcccaacaacg</td>
<td>ttcctctcaaagcttgtgcccac</td>
</tr>
<tr>
<td>Ckap4</td>
<td>ggaggaggctccagcagtt</td>
<td>ttgcaggagatgcctccctt</td>
</tr>
<tr>
<td>Cnn3</td>
<td>cgcctgaagtttgaagaacag</td>
<td>ggctgtcaccctctcttctcc</td>
</tr>
<tr>
<td>Cnnp</td>
<td>gcgcgggcaagaagaatctc</td>
<td>aaggcctttgccatcaacctt</td>
</tr>
<tr>
<td>Cntnap1</td>
<td>ggcgcggaagctctgctcattc</td>
<td>agttcaaccttgccagagagc</td>
</tr>
<tr>
<td>Col1a2</td>
<td>gcaggtctcactctcttgctc</td>
<td>cttgcacacttcatcttgttt</td>
</tr>
<tr>
<td>Cplx2</td>
<td>acctgctgctccacttggtagc</td>
<td>ctgccttgggaaagtgagc</td>
</tr>
<tr>
<td>Crh</td>
<td>ggaggcatctctgagagaagtc</td>
<td>catgttaggggcgctctc</td>
</tr>
<tr>
<td>Crys3</td>
<td>tggggcactgataaaagttgt</td>
<td>tgggaaaatggggcttctcata</td>
</tr>
<tr>
<td>Cyp11a1</td>
<td>catctcaacattggcagagtg</td>
<td>ggttcacgctcagggtcat</td>
</tr>
<tr>
<td>Cyp17a1</td>
<td>cccctcagcccaaccaaaag</td>
<td>cagttccagcagattgtagta</td>
</tr>
<tr>
<td>Cyp19a1</td>
<td>ccactctctgctatagctg</td>
<td>tccacagaccacaccagac</td>
</tr>
<tr>
<td>Ddit4</td>
<td>ccagaagaagggcccttga</td>
<td>ccatccagagtacagttcctt</td>
</tr>
<tr>
<td>Dhc24</td>
<td>tcatgatcaacgtgagagcag</td>
<td>gcctcactgcaaatcatcg</td>
</tr>
<tr>
<td>Erb5b</td>
<td>tggagaagagagagctctctc</td>
<td>cagcatcgatcatcacaacca</td>
</tr>
<tr>
<td>Ext5</td>
<td>ggtggtctgctactcagcgct</td>
<td>ttgaactaatggacaccagac</td>
</tr>
<tr>
<td>Fgf1</td>
<td>cagctgtgccaggttcttcag</td>
<td>ggcgcggaaggtgggtgtgat</td>
</tr>
<tr>
<td>Fgf1r1</td>
<td>gacgtctgcctctacctgctg</td>
<td>agagtgagggagtcacgctga</td>
</tr>
<tr>
<td>Fshb</td>
<td>gtgcctcacttggtaaatgct</td>
<td>tgggtctcataccacagatcc</td>
</tr>
<tr>
<td>Fshr</td>
<td>tgcgctgtagcttcttcaggct</td>
<td>gcgggaagtagaccttctgc</td>
</tr>
<tr>
<td>Fzd5</td>
<td>cagcaggacttcctcggaga</td>
<td>cagcactcgatctccacacca</td>
</tr>
<tr>
<td>Gal3s3</td>
<td>gggagcctcctgcacacgact</td>
<td>ctgggtaggggcccaggt</td>
</tr>
<tr>
<td>Gata2</td>
<td>tcccccctaagcagaggaac</td>
<td>cagccatctcagagggagt</td>
</tr>
<tr>
<td>Gh</td>
<td>gcctggcatgtgcacagcaga</td>
<td>ggagaacacclaggtccttg</td>
</tr>
<tr>
<td>Ghrh</td>
<td>cagggagagctctgagacg</td>
<td>aggtttccatttgaggaatc</td>
</tr>
<tr>
<td>Gic1</td>
<td>gggttaacaggagttggtgta</td>
<td>ctagcatgagctgagaggaag</td>
</tr>
<tr>
<td>Glg1</td>
<td>gcagcggtcctctcttcttct</td>
<td>ggctctcactccccactcctc</td>
</tr>
<tr>
<td>Glil</td>
<td>ctgactctgccccagaggttg</td>
<td>cgctgtgcacagaggactcct</td>
</tr>
<tr>
<td>Glil2</td>
<td>gcagactgaccacagaggttga</td>
<td>cgfgagatglgtctctgaggct</td>
</tr>
<tr>
<td>Glil3</td>
<td>gcgcctccagcatggagcctg</td>
<td>gcgtgaaagctggcaccagag</td>
</tr>
<tr>
<td>Gmnh</td>
<td>tcagggatctgccccgagag</td>
<td>ggccgagctgtcatcatacg</td>
</tr>
<tr>
<td>Gpr54</td>
<td>ggtgtctggagacctagtctg</td>
<td>agttgcacatgggtgcttg</td>
</tr>
<tr>
<td>Orem1</td>
<td>gaccacaggaagttgacaga</td>
<td>cccctcagcttgccagctcag</td>
</tr>
<tr>
<td>Hes1</td>
<td>acaccocgcaaaaccaacagc</td>
<td>cgcctctctctcaagattcaga</td>
</tr>
<tr>
<td>Hes6a1</td>
<td>ggacgcaactcacaacagcct</td>
<td>cgcagcaggggtgtggttagt</td>
</tr>
<tr>
<td>Hsd17b1</td>
<td>gtgggtgagctctgtgagagg</td>
<td>gcgtcctagtggtcattccagac</td>
</tr>
<tr>
<td>Hsd17b2</td>
<td>tccaccaagcagagacgata</td>
<td>gttaccacgcctccacagctg</td>
</tr>
<tr>
<td>Hsd17b3</td>
<td>aataatgtcagctgagcttgct</td>
<td>gaaggagatcggttcaaaatg</td>
</tr>
<tr>
<td>Hsd3b1</td>
<td>gaccagaaaacacaggaagag</td>
<td>gcacgctgccatccagatga</td>
</tr>
<tr>
<td>Hsd3b6</td>
<td>agactggagctgtgagccacc</td>
<td>caggaacacatcagcaaggattg</td>
</tr>
<tr>
<td>Igsf8</td>
<td>gcaggggagctgtgagccgct</td>
<td>gtcagttggagcttgagc</td>
</tr>
<tr>
<td>Irs4</td>
<td>acggcctagggtagtction</td>
<td>ctttgtgggctcttctccttc</td>
</tr>
<tr>
<td>Isi1</td>
<td>gcacgcccaacagacaaactctaa</td>
<td>ccatactctctccgggactcct</td>
</tr>
<tr>
<td>Kiss1</td>
<td>aagctcgtggagctctcag</td>
<td>cccctcctccctctctctctg</td>
</tr>
<tr>
<td>Kcnj2</td>
<td>tgaagttgcctcataacgaca</td>
<td>gttccctggagacctgtctct</td>
</tr>
<tr>
<td>Klf13a</td>
<td>cccctctagctcttgaagaaga</td>
<td>ttctctctctgctctctctct</td>
</tr>
<tr>
<td>Kiss1</td>
<td>aatgtctcaagttgctctgg</td>
<td>ccaggcattaaacaggtgctc</td>
</tr>
<tr>
<td>Gene</td>
<td>Forward Primer</td>
<td>Reverse Primer</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Lepr</td>
<td>gttcacaacaaccaagaattg</td>
<td>tgcctaaatgtgtcaccgtt</td>
</tr>
<tr>
<td>Lhb</td>
<td>caagaatggagaggctccag</td>
<td>actgggccaaacttccttcg</td>
</tr>
<tr>
<td>Lh3x4</td>
<td>agacagccaaagacacgat</td>
<td>ggctttgggagttcttgta</td>
</tr>
<tr>
<td>Mapk4</td>
<td>tcacggggaatgcctt</td>
<td>cagggatggtgtctaggaatga</td>
</tr>
<tr>
<td>Mknk2</td>
<td>cglttgccagactgtgca</td>
<td>ccagctgctctcaatgtactc</td>
</tr>
<tr>
<td>Mom4</td>
<td>aggcacaagcagcaaatagat</td>
<td>tggagccagctcacagagaagaac</td>
</tr>
<tr>
<td>Nelf</td>
<td>ccacaactgtcaagcctcatc</td>
<td>cggaaatctttccctctttgtt</td>
</tr>
<tr>
<td>Nlfb</td>
<td>ccgaaaactctggagtagag</td>
<td>gaaatggccaaacttccttcg</td>
</tr>
<tr>
<td>Nr5a1</td>
<td>agcactctgtcttgatatgg</td>
<td>gcatacctggagactacacctgcgtc</td>
</tr>
<tr>
<td>Orai1</td>
<td>ttactgacccgcccaag</td>
<td>acttcacacatgctacaccc</td>
</tr>
<tr>
<td>Pbx3</td>
<td>gcctgagcacaactctgctgtag</td>
<td>gagtaagttggaggtggctgctc</td>
</tr>
</tbody>
</table>
| Pln2  | gtgcacgttggagacaaacagagagcagcagagagcagctcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcagcagagagcаг
<table>
<thead>
<tr>
<th>Gene</th>
<th>Sequence 1</th>
<th>Sequence 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acvr1</td>
<td>gttggaagattacaagccacca</td>
<td>ggggcttgagaacacactctgtttagg</td>
</tr>
<tr>
<td>Acvr1b</td>
<td>ggcggctcaagtgcacccataga</td>
<td>gaggccttcctgtgagcgcaga</td>
</tr>
<tr>
<td>Acvr1c</td>
<td>tggtaacacaagatcacatcagttg</td>
<td>cacgtgagtgcaccttgttaaa</td>
</tr>
<tr>
<td>Acvr2a</td>
<td>gggaggtatctgagggaga</td>
<td>tctcgaggcaactctactca</td>
</tr>
<tr>
<td>Acvr2b</td>
<td>cgacttttgtggctgtgaaga</td>
<td>tcgtgccacggtgatgtgt</td>
</tr>
<tr>
<td>Egr1</td>
<td>tcctctccatatcatgccttg</td>
<td>cactcagcactgtctccag</td>
</tr>
<tr>
<td>Foxl2</td>
<td>gggaggagaatgtgaattgg</td>
<td>cagagcctaatgaagtcacc</td>
</tr>
<tr>
<td>Smad1</td>
<td>cgctccagggccacagttgaag</td>
<td>gcaggtgtatggcaacagaa</td>
</tr>
<tr>
<td>Smad2</td>
<td>aacccggaatgtgcacccataag</td>
<td>gcaggtcctttgatgggttaacga</td>
</tr>
<tr>
<td>Smad3</td>
<td>gtcaacaaatgtgtggccttgflgl</td>
<td>gcagcgaagctctgggataa</td>
</tr>
<tr>
<td>Smad4</td>
<td>ggacgcctaaaccattttcag</td>
<td>cgcgaagcagcaagcagcaaac</td>
</tr>
<tr>
<td>Smad5</td>
<td>tgcagcttgagacgctctcacc</td>
<td>gcagaacctacaglgccagccatc</td>
</tr>
<tr>
<td>Smad6</td>
<td>ttcctggtctgtctctccta</td>
<td>gggccctgggttctgtgatgaaga</td>
</tr>
<tr>
<td>Smad7</td>
<td>ggctatccacagcctctcaga</td>
<td>ggcacagccgcagcagtaagca</td>
</tr>
<tr>
<td>Smad9</td>
<td>cgatctccataagactgacaa</td>
<td>tgggcaagccaaaccgata</td>
</tr>
</tbody>
</table>