Supplemental Data 1. Walker et al.

CALCULATING BAYES FACTORS FOR THE GENE EXPRESSION DATA

1. What Are Bayes Factors Computing

Bayes factors are a Bayesian approach to model selection. Unlike hypothesis testing, which decides whether to reject a null hypothesis at some predetermined significance level, Bayes factors measure the evidence for one model $M_1(\theta_1)$ against another model $M_2(\theta_2)$. If we denote the data by D, then the Bayes factor is given by

$$K = \frac{P(D|M_1)}{P(D|M_2)} = \frac{\int P(D|M_1, \theta_1)\, d\theta_1}{\int P(D|M_2, \theta_2)\, d\theta_2}$$

(we assume uniform priors). A ratio greater than 1 means that M_1 has more support, given the data, than M_2. A ratio less than 1 means the opposite. To "normalize" the Bayes factor, a logarithm is often taken so that 0 indicates no preference between the models, and so that a positive number indicates the same strength of evidence for M_1 as the negative equivalent indicates for M_2. A base of 10 is often chosen, and then $\log_{10} K$ is measured in "decibans."

We want to decide whether gene expression levels between two groups look like they are generated by one or two distributions. In other words, we want to decide whether or not the two groups exhibit differentiable gene expression levels. We assume the data are generated by a normal distribution. For our M_1, we assume the data for two groups are generated by different normal distributions (different mean and variance). For M_2, we assume the data for both groups are generated by the same normal distribution.

2. Probability Of Data From The Same Normal Distribution

Let N be the number of data points, and denote the data points by $x_1, \ldots, x_N$. The probability of $x_1, \ldots, x_N$ all being generated from the same normal distribution $N(\mu, \sigma)$ is:

$$P(x_1, \ldots, x_N|\mu, \sigma) = \prod_i P(x_i|\mu, \sigma).$$

To marginalize over the distribution parameters, we need to integrate this product over the parameters μ, σ. Rewriting the product to separate the parameters will allow us to calculate the integral. We start with

$$\begin{aligned}\prod_i P(x_i|\mu, \sigma) &= \prod_i \frac{1}{\sigma\sqrt{2\pi}} e^{\frac{(x-u_i)^2}{2\sigma^2}} \\ &= \frac{1}{\left(\sigma\sqrt{2\pi}\right)^N} \exp\left\{-\frac{1}{2\sigma^2}\sum_i (x_i - \mu)^2\right\}.\end{aligned}$$

Let's just work on the exponential, so

$$\begin{aligned}\exp\left\{-\frac{1}{2\sigma^2}\sum_i(x_i-\mu)^2\right\} &= \exp\left\{-\frac{1}{2\sigma^2}\left[\mu^2-2\mu x_1+x_1^2+\mu^2-2\mu x_2+x_2^2+\cdots\right]\right\}\\ &= \exp\left\{-\frac{1}{2\sigma^2}\left[N\mu^2-2\mu\left(\sum x_i\right)+\sum x_i^2\right]\right\}\\ &= \exp\left\{-\frac{N}{2\sigma^2}\left[\mu^2-2\mu\bar{x}+\sum\frac{x_i^2}{N}\right]\right\},\end{aligned}$$

where $\bar{x}$ is the average of the data points. This exponential almost looks like a Gaussian (which we know how to integrate), except that the term in the brackets isn't a square. So we complete the square:

$$\begin{aligned}&= \exp\left\{-\frac{N}{2\sigma^2}\left[\mu^2-2\mu\bar{x}+\bar{x}^2+\left(\sum\frac{x_i^2}{N}\right)-\bar{x}^2\right]\right\}\\ &= \exp\left\{-\frac{N}{2\sigma^2}(\mu-\bar{x})^2\right\}\exp\left\{-\frac{N}{2\sigma^2}\left(\sum\frac{x_i^2}{N}-\bar{x}^2\right)\right\}.\end{aligned}$$

Note that $\left(\sum\frac{x_i^2}{N}-\bar{x}^2\right)$ is a constant; let's abbreviate it as κ.

Now we just use u-substitution to compute the integral:

$$\int_{\mathbb{R}} P(x_1,\ldots,x_N|\mu,\sigma)\,d\mu = \frac{1}{\left(\sigma\sqrt{2\pi}\right)^N}\exp\left\{-\frac{N\kappa}{2\sigma^2}\right\}\int_{\mathbb{R}}\exp\left\{-\frac{N}{2\sigma^2}(\mu-\bar{x})^2\right\}d\mu$$

let $u=\sqrt{\frac{N}{2\sigma^2}}(\mu-\bar{x})$ so $du=\sqrt{\frac{N}{2\sigma^2}}\,d\mu$, then

$$\begin{aligned}&= \frac{1}{\left(\sigma\sqrt{2\pi}\right)^N}\exp\left\{-\frac{N\kappa}{2\sigma^2}\right\}\sqrt{\frac{2\sigma^2}{N}}\int_{\mathbb{R}}e^{-u^2}du\\ &= \frac{1}{\left(\sigma\sqrt{2\pi}\right)^N}\exp\left\{-\frac{N\kappa}{2\sigma^2}\right\}\sqrt{\frac{2\pi\sigma^2}{N}}\\ &= \frac{1}{\sqrt{N}\left(\sigma\sqrt{2\pi}\right)^{N-1}}\exp\left\{-\frac{N\kappa}{2\sigma^2}\right\}.\end{aligned}$$

Now we can integrate this expression with respect to σ. The integral has the same basic form as

$$\int_0^\infty \frac{1}{x^{N-1}\,e^{1/x^2}}dx = \frac{1}{2}\Gamma\left(\frac{N}{2}-1\right) \quad \text{for} \quad N>2,$$

(here $\Gamma(x)$ is the gamma function). Using u-substitution with $u = \sigma\sqrt{\frac{2}{N\kappa}}$, so $du = \sqrt{\frac{2}{N\kappa}}\, d\sigma$, we have

$$\begin{aligned}
&\int_0^\infty \int_{\mathbb{R}} P(x_1, \ldots, x_N|\mu, \sigma)\, d\mu\, d\sigma \\
&\qquad = \frac{1}{\sqrt{N}(\sqrt{2\pi})^{N-1}} \int_0^\infty \frac{1}{\sigma^{N-1}} \cdot \exp\left\{-\frac{N\kappa}{2\sigma^2}\right\} d\sigma \\
&\qquad = \frac{1}{\sqrt{N}(\sqrt{2\pi})^{N-1}} \left(\sqrt{\frac{2}{N\kappa}}\right)^{N-2} \int_0^\infty \frac{1}{u^{N-1}\, e^{1/u^2}}\, du \\
&\qquad = \frac{1}{\sqrt{N}(\sqrt{2\pi})^{N-1}} \left(\sqrt{\frac{2}{N\kappa}}\right)^{N-2} \Gamma\left(\frac{N}{2} - 1\right).
\end{aligned}$$

Note that this expression has no dependence on the distribution parameters, and depends solely on the data points, as we would expect.

3. Probability Of Data From Two Normal Distributions

Now suppose we have data from two groups, say $x_1, \ldots, x_N$ from group A, and $y_1, \ldots, y_M$ from group B. The probability that the x_i are generated by a normal distribution $N(\mu_A, \sigma_A)$, and that the y_j are generated by a normal distribution $N(\mu_B, \sigma_B)$ is:

$$\begin{aligned}
&P(x_1, \ldots, x_N, y_1, \ldots, y_M|\mu_a, \sigma_A, \mu_B, \sigma_B) \\
&\qquad\qquad = P(x_1, \ldots, x_N|\mu_A, \sigma_A) \cdot P(y_1, \ldots, y_M|\mu_B, \sigma_B)
\end{aligned}$$

(since two groups are independent of each other)

$$= \prod_i P(x_i|\mu_A, \sigma_A) \cdot \prod_j P(y_j|\mu_B, \sigma_B).$$

So marginalizing over the parameters is simply:

$$\begin{aligned}
&\int P(x_1, \ldots, x_N, y_1, \ldots, y_M|\mu_a, \sigma_A, \mu_B, \sigma_B)\, d\mu_A\, d\sigma_A\, d\mu_B\, d\sigma_B \\
&\quad = \int \prod_i P(x_i|\mu_A, \sigma_A) \cdot \prod_j P(y_j|\mu_B, \sigma_B)\, d\mu_A\, d\sigma_A\, d\mu_B\, d\sigma_B \\
&\quad = \int_0^\infty \int_{\mathbb{R}} \prod_i P(x_i|\mu_A, \sigma_A)\, d\mu_A\, d\sigma_A \cdot \int_0^\infty \int_{\mathbb{R}} \prod_j P(y_j|\mu_B, \sigma_B)\, d\mu_B\, d\sigma_B,
\end{aligned}$$

and we can calculate each factor by simply using the formula in the previous section.

4. Interpreting The Bayes Factors

If K is the Bayes factor, let $B = \log_{10} K$, with B measured in decibans. Positive B is evidence for M_1, that data for the two groups is generated by different normal distributions.

Important to note is that M_2 (one normal distribution) is a special case of M_1 (two normal distribution), where the means and variances are equal. Thus B will never be very negative, as evidence for M_2 is not inconsistent with M_1. It *is* possible for B to be negative, as Bayes factors have a slight preference for models with fewer parameters, which provides some protection from overfitting.

Supplemental Data 2. Walker et al.

AREA BETWEEN PIECEWISE-LINEAR CURVES

1. Setup

A *piecewise-linear curve* is a curve specified by a sequence of points $(P_1, \dots, P_n)$, where neighboring points in the sequence are connected by a line segment. For our purposes, we will only be dealing with curves that are piecewise-linear, and henceforth "curve" will mean "piecewise-linear curve."

We assume that for a finite number of x-values, we are given two y-values: a_i and b_i. For ever x_i we have the points (x_i, a_i) and (x_i, b_i), and the two respective curves A and B. It suffices to choose two x-values x_i and x_{i+1}, and compute the area between A and B over this interval, as the total area will be the sum of the areas over such intervals. The curves over the interval $[x_i, x_{i+1}]$ are completely determined by the points (x_i, a_i), (x_i, b_i), (x_{i+1}, a_{i+1}), and (x_{i+1}, b_{i+1}), and we will express the area in terms of these values. There are two cases: A and B intersect over the interval $[x_i, x_{i+1}]$, or not.

2. A and B Do Not Intersect

To simplify notation, we assume $i = 1$, and without loss of generality, we assume $a_1 > b_1$ and $a_2 > b_2$. To find the are between A and B we will compute an integral, but we need equations for A and B over $[x_1, x_2]$ to do that. The slope of A is $\frac{a_2 - a_1}{x_2 - x_1}$, thus the equation for A over $[x_1, x_2]$ is

$$\begin{aligned} y - a_1 &= \left(\frac{a_2 - a_1}{x_2 - x_1}\right)(x - x_1) \\ y &= \left(\frac{a_2 - a_1}{x_2 - x_1}\right) x - \left(\frac{a_2 - a_1}{x_2 - x_1}\right) x_1 + a_1. \end{aligned}$$

Using an integral to compute the are between A and B over $[x_1, x_2]$,

$$\begin{aligned} &\int_{x_1}^{x_2} \left(\frac{a_2 - a_1 - b_2 + b_1}{x_2 - x_1}\right) x - x_1 \left(\frac{a_2 - a_1 - b_2 + b_1}{x_2 - x_1}\right) + (a_1 - b_1)\, dx \\ &\quad = \left[\frac{1}{2}\left(\frac{a_2 - a_1 - b_2 + b_1}{x_2 - x_1}\right) x^2 - x_1 \left(\frac{a_2 - a_1 - b_2 + b_1}{x_2 - x_1}\right) x + (a_1 - b_1)x\right]_{x_1}^{x_2} \\ &\quad = \frac{1}{2}(a_2 - a_1 - b_2 + b_1)(x_2 + x_1) - x_1(a_2 - a_1 - b_2 + b_1) + (a_1 - b_1)(x_2 - x_1) \\ &\quad = \frac{1}{2}(a_2 + a_1 - b_2 - b_1)(x_2 - x_1). \end{aligned}$$

This expression can be written as:

$$\frac{1}{2} \cdot \frac{-(a_1 - b_1)^2 + (a_2 - b_2)^2}{a_2 - a_1 - b_2 + b_1}(x_2 - x_1).$$

Why one would want to make the expression more complex will become clear in the next section.

3. A and B Do Intersect

We use the same simplifying assumptions as above, except we assume $a_1 > b_1$ and $a_2 < b_2$. In this case, the are between A and B is the sum of the areas of two triangles. We can use the ordinary area formula for a triangle after we find the intersection point of A and B. At the intersection point $(x_{\text{int}}, y_{\text{int}})$, the y-values are equal, so:

$$\begin{aligned}
\left(\frac{a_2 - a_1}{x_2 - x_1}\right) x_{\text{int}} - x_1 \left(\frac{a_2 - a_1}{x_2 - x_1}\right) + a_1 &= \left(\frac{b_2 - b_1}{x_2 - x_1}\right) x_{\text{int}} - x_1 \left(\frac{b_2 - b_1}{x_2 - x_1}\right) + b_1 \\
\left(\frac{a_2 - a_1 - b_2 + b_1}{x_2 - x_1}\right) x_{\text{int}} &= x_1 \left(\frac{a_2 - a_1 - b_2 + b_1}{x_2 - x_1}\right) + (b_1 - a_1) \\
x_{\text{int}} &= x_1 + \left(\frac{x_2 - x_1}{a_2 - a_1 - b_2 + b_1}\right)(b_1 - a_1).
\end{aligned}$$

Now the sum of the areas of the triangles is:

$$\begin{aligned}
&\frac{1}{2}(a_1 - b_1)(x_{\text{int}} - x_1) + \frac{1}{2}(b_2 - a_2)(x_2 - x_{\text{int}}) \\
&= \frac{1}{2} \cdot \frac{(a_1 - b_1)(b_1 - a_1)}{a_2 - a_1 - b_2 + b_1}(x_2 - x_1) + \frac{1}{2} \cdot \frac{(b_2 - a_2)(a_2 - b_2)}{a_2 - a_1 - b_2 + b_1}(x_2 - x_1) \\
&= \frac{1}{2} \cdot \frac{-(a_1 - b_1)^2 - (a_2 - b_2)^2}{a_2 - a_1 - b_2 + b_1}(x_2 - x_1).
\end{aligned}$$

This expression is nearly identical to the one above, differing by a change of sign in the numerator.

Supplemental Table 1. Expression of 48 genes in the AVPV.

Gene Symbol	Gene Name	Statistic	Sex	Age	Trt	Sex X Age	Sex X Trt	Age X Trt	Sex X Age X Trt	Female - DMSO P15	Female - DMSO P30	Female - DMSO P45	Female - DMSO P90	Female - EB P15	Female - EB P30	Female - EB P45	Female - EB P90	Female - A1221 P15	Female - A1221 P30	Female - A1221 P45	Female - A1221 P90
Females			**Females-Statistical Results (MR)**							**Female - DMSO**				**Female - EB**				**Female - A1221**			
18s	Eukaryotic 18S RNA, 18S ribosomal 1	MR	0.131	**0.041**	0.891	0.732	0.242	0.425	0.862	1.35	1.40	1.34	1.35	1.58	1.36	1.33	1.25	1.44	1.20	1.35	1.15
Ar	androgen receptor	MR	0.727	**0.000**	0.502	0.235	0.839	0.030	0.035	2.33	2.86	3.26	4.10	1.04	3.34	4.99	5.81	1.32	3.69	3.89	6.83
Arntl	aryl hydrocarbon receptor nuclear translocator-like	MR	0.285	**0.000**	0.846	0.050	0.345	0.260	**0.011**	1.70	1.58	1.41	1.45	0.99	1.44	1.91	1.95	1.19	1.48	1.50	1.80
Avpr1a	arginine vasopressin receptor 1A	MR	**0.002**	**0.000**	0.468	0.672	0.478	0.128	0.024	2.05	1.65	1.60	1.92	1.03	1.67	2.43	2.42	1.42	1.74	2.00	2.45
Bdnf	brain-derived neurotrophic factor	MR	0.106	**0.007**	0.795	0.604	0.015	0.192	0.150	1.67	1.15	1.29	1.27	1.24	1.32	2.20	1.94	1.10	1.45	1.64	2.02
Cyp19a1	cytochrome P450, family 19, subfamily A, polypeptide 1	MR	0.743	**0.000**	0.408	0.627	0.120	0.219	0.652	2.37	1.85	2.13	2.46	1.20	2.43	3.70	4.40	1.49	2.18	3.37	5.00
Dnmt1	DNA (cytosine-5-)-methyltransferase 1	MR	0.979	**0.003**	0.785	0.198	0.696	0.084	**0.002**	2.25	1.60	1.52	1.28	1.25	1.55	1.88	2.03	1.49	1.62	1.39	2.11
Dnmt3a	DNA (cytosine-5-)-methyltransferase 3a	MR	0.110	**0.000**	0.814	0.117	0.699	0.608	0.278	9.43	1.90	1.39	1.03	5.59	1.85	1.90	1.37	6.19	1.92	1.20	1.29
Esr1	estrogen receptor 1	MR	0.726	**0.000**	0.284	0.600	0.191	0.053	0.530	3.66	3.50	2.73	3.96	1.02	5.08	4.66	7.07	1.94	4.48	4.89	7.22
Esr2	estrogen receptor 2	MR	0.067	**0.000**	0.922	0.461	0.084	0.178	0.094	1.91	1.81	2.58	3.41	1.06	2.72	4.42	4.66	1.23	2.39	3.71	4.26
Gapdh	glyceraldehyde-3-phosphate dehydrogenase	MR	0.438	**0.000**	0.985	0.457	0.694	0.501	0.029	1.80	1.84	1.69	1.56	1.10	1.72	2.24	2.21	1.30	1.89	1.48	2.07
Gper	G protein-coupled estrogen receptor 1	MR	0.828	0.120	0.927	0.199	0.540	**0.003**	0.027	2.22	1.18	1.07	1.01	1.13	1.67	1.55	1.37	1.32	1.38	1.40	1.16
Gria1	glutamate receptor, ionotropic, AMPA 1	MR	0.417	**0.000**	0.909	0.084	0.216	0.580	0.212	1.44	1.63	1.27	1.38	1.13	1.56	1.86	1.90	1.13	1.45	1.38	1.70
Grin1	glutamate receptor, ionotropic, N-methyl D-aspartate 1	MR	0.569	**0.023**	0.471	0.199	0.431	0.437	**0.011**	1.54	1.30	1.27	1.15	1.16	1.40	1.67	1.62	1.50	1.44	1.28	1.61
Grin2b	glutamate receptor, ionotropic, N-methyl D-aspartate 2B	MR	0.622	**0.000**	0.546	0.290	0.684	0.817	0.075	2.30	1.25	1.39	1.36	1.80	1.44	1.85	1.70	1.82	1.40	1.32	1.77
Grin2c	glutamate receptor, ionotropic, N-methyl D-aspartate 2C	MR	0.410	**0.000**	0.460	0.068	0.727	0.721	0.085	1.32	1.69	2.00	1.58	1.01	1.70	2.17	1.97	1.04	1.67	1.65	1.91
Grin2d	glutamate receptor, ionotropic, N-methyl D-aspartate 2D	MR	0.260	**0.000**	0.749	0.189	0.798	0.611	**0.017**	2.32	1.51	1.49	1.34	1.70	1.72	1.93	1.82	2.26	1.83	1.39	1.77
Igf1r	insulin-like growth factor 1 receptor	MR	0.345	**0.000**	0.857	0.353	0.382	0.113	**0.031**	1.38	1.51	1.55	1.24	0.99	1.43	1.87	1.88	1.11	1.49	1.40	1.90
Kiss1r	KISS1 receptor	MR	0.148	**0.000**	0.755	0.626	0.587	0.133	**0.006**	2.02	1.51	1.66	2.22	0.90	1.86	2.92	3.34	1.19	2.11	2.14	2.47
Mc3r	melanocortin 3 receptor	MR	0.282	**0.000**	0.839	0.952	0.010	0.268	0.100	2.77	2.84	3.35	3.46	1.27	3.57	5.84	6.20	1.85	2.97	4.02	5.08
Mc4r	melanocortin 4 receptor	MR	0.096	**0.000**	0.457	0.141	0.657	0.731	0.168	1.58	2.19	2.13	3.00	1.12	1.92	3.56	3.99	1.14	2.21	2.92	3.22
Oxtr	oxytocin receptor	MR	0.922	**0.000**	0.961	0.298	0.801	0.224	0.241	2.68	1.22	1.55	1.52	1.53	1.45	2.14	2.08	1.95	1.39	1.49	2.01
Pdyn	prodynorphin	MR	0.197	**0.000**	0.402	0.495	0.012	0.121	0.056	1.74	1.63	2.43	2.50	0.85	2.31	4.11	3.84	1.32	2.05	2.87	3.05
Per2	period homolog 2	MR	0.248	**0.000**	0.636	0.913	0.006	0.448	**0.006**	1.79	1.85	2.02	2.11	1.00	2.41	3.22	3.55	1.30	2.21	2.36	2.94
Pgr	progesterone receptor	MR	0.805	**0.000**	0.357	0.420	0.145	0.531	0.579	1.42	1.57	2.60	3.37	1.06	2.04	4.65	5.04	1.26	1.98	3.69	4.70
Slc17a6	solute carrier family 17, member 6	MR	0.378	**0.000**	0.253	0.895	0.010	0.101	0.126	1.39	0.93	1.14	1.40	0.91	1.39	1.96	1.82	1.07	1.36	1.77	1.81
Srd5a1	steroid-5-alpha-reductase, alpha polypeptide 2	MR	0.897	**0.000**	0.233	0.102	0.539	0.473	0.067	1.48	1.84	2.50	1.42	1.06	1.55	2.09	1.73	1.12	1.83	1.15	1.56
Tgfa	transforming growth factor, alpha	MR	0.889	**0.000**	0.969	0.553	0.272	0.649	**0.007**	1.70	1.22	1.60	1.32	1.09	1.29	1.96	1.93	1.23	1.37	1.27	1.77
Tgfb1	transforming growth factor, beta 1	MR	0.979	0.068	0.410	0.244	0.763	0.708	0.098	2.45	1.36	1.42	1.11	1.71	1.61	1.92	1.53	1.58	1.76	1.39	1.61
Thra	thyroid hormone receptor, alpha	MR	0.835	0.087	0.728	0.124	0.162	0.419	**0.001**	1.85	1.62	1.51	1.18	1.18	1.66	2.00	1.93	1.32	1.65	1.25	1.67
Thrb	thyroid hormone receptor, beta	MR	0.353	**0.000**	0.980	0.242	0.555	0.344	0.103	1.74	1.97	2.08	1.85	1.26	2.00	2.49	2.31	1.14	1.92	1.69	2.40
			Females-Statistical Results (NP)							**Female - DMSO**				**Female - EB**				**Female - A1221**			
Ahr	aryl hydrocarbon receptor	NP	0.410	**0.000**	0.432	**0.000**	0.693	**0.000**	**0.000**	4.13	2.35	2.10	1.08	3.16	2.07	1.83	1.32	3.43	1.92	1.31	1.08
Avp	arginine vasopressin	NP	0.743	**0.000**	0.353	**0.002**	0.420	**0.002**	**0.015**	4.97	1.33	3.19	3.70	1.12	2.66	5.10	9.11	1.15	2.20	2.67	4.78
Gad1	glutamate decarboxylase 1 (brain, 67kDa)	NP	0.634	0.346	0.988	0.256	0.923	0.485	0.130	1.57	1.77	1.90	1.47	0.98	1.51	1.77	1.73	1.46	1.64	1.10	1.62
Gad2	glutamate decarboxylase 2 (pancreatic islets and brain, 65kDa)	NP	0.437	**0.037**	0.936	0.057	0.913	0.104	0.030	1.57	1.63	1.50	1.45	0.98	1.43	1.79	1.72	1.38	1.41	1.22	1.76
Gal	galanin prepropeptide	NP	0.995	**0.000**	0.799	**0.000**	0.308	**0.000**	**0.000**	2.16	2.13	4.00	3.91	1.02	4.58	7.45	7.59	1.40	3.65	4.99	5.85
Gnrh1	gonadotropin-releasing hormone 1	NP	0.790	**0.000**	0.944	**0.000**	0.711	**0.000**	**0.000**	2.26	2.07	3.30	3.71	1.11	2.87	6.42	5.26	1.53	3.18	3.84	5.08
Gria2	glutamate receptor, ionotropic, AMPA 2	NP	0.938	0.079	0.856	0.112	0.832	0.375	0.057	1.56	1.60	1.07	1.13	1.11	1.30	1.54	1.59	1.18	1.28	1.21	1.38
Grik2	glutamate receptor, ionotropic, kainate 2	NP	0.942	**0.003**	0.630	**0.002**	0.808	0.081	**0.019**	1.78	1.82	1.27	1.21	1.15	1.30	1.37	1.27	1.45	1.32	1.05	1.33
Grin2a	glutamate receptor, ionotropic, N-methyl D-aspartate 2A	NP	0.484	0.323	0.697	0.509	0.559	0.790	0.553	1.56	1.33	1.36	1.22	1.56	1.48	1.43	1.58	1.35	1.36	1.06	1.52
Igf1	insulin-like growth factor 1	NP	0.016	**0.000**	0.617	**0.000**	0.227	**0.000**	**0.000**	2.61	1.47	1.76	1.34	1.83	1.29	1.82	2.05	2.46	1.28	1.31	1.75
Kiss1	KiSS-1 metastasis-suppressor	NP	**0.000**	**0.000**	0.266	**0.000**	**0.001**	**0.000**	**0.000**	5.08	6.45	15.26	10.17	3.10	11.06	20.41	25.88	2.74	12.37	20.25	21.23
Lepr	leptin receptor	NP	0.431	**0.000**	0.846	**0.000**	0.943	**0.000**	**0.000**	2.20	2.03	2.00	2.99	1.24	2.19	2.39	3.78	1.20	1.84	2.60	3.68
Oxt	oxytocin, prepropeptide	NP	0.900	**0.000**	0.730	**0.000**	0.644	0.000	**0.000**	2.70	4.75	15.98	9.20	1.15	7.69	26.01	42.06	1.17	11.97	9.82	13.23
Tac2	tachykinin 2	NP	0.100	**0.000**	0.903	**0.000**	0.605	**0.002**	**0.006**	1.54	1.96	1.93	1.77	1.01	1.65	2.92	3.29	1.56	1.19	1.43	2.65
Dnmt3l	DNA (cytosine-5-)-methyltransferase 3l	N/A																			
Gnrhr	gonadotropin-releasing hormone receptor	N/A																			
Mc5r	melanocortin5 receptor	N/A																			

Males			Males-Statistical Results (MR)							Male - DMSO				Male - EB				Male - A1221			
Gene Symbol	Gene Name	Statistic	Sex	Age	Trt	Sex X Age	Sex X Trt	Age X Trt	Sex X Age X Trt	P15	P30	P45	P90	P15	P30	P45	P90	P15	P30	P45	P90
18s	Eukaryotic 18S RNA, 18S ribosomal 1	MR	0.131	**0.041**	0.891	0.732	0.242	0.425	0.862	1.30	1.36	1.20	1.15	1.41	1.45	1.20	1.09	1.38	1.29	1.37	1.36
Ar	androgen receptor	MR	0.727	**0.000**	0.502	0.235	0.839	0.030	0.035	1.19	3.82	3.86	5.82	1.17	2.80	4.46	5.33	1.17	2.44	4.95	6.91
Arntl	aryl hydrocarbon receptor nuclear translocator-like	MR	0.285	**0.000**	0.846	0.050	0.345	0.260	**0.011**	1.11	1.31	1.45	2.12	1.19	1.09	1.43	1.78	1.27	1.18	1.70	1.92
Avpr1a	arginine vasopressin receptor 1A	MR	**0.002**	**0.000**	0.468	0.672	0.478	0.128	0.024	1.28	1.67	1.47	1.96	1.33	1.25	1.45	1.72	1.54	1.34	2.04	1.86
Bdnf	brain-derived neurotrophic factor	MR	0.106	**0.007**	0.795	0.604	0.015	0.192	0.150	1.44	1.50	1.42	1.66	1.21	1.00	1.34	1.26	1.49	1.07	1.61	1.56
Cyp19a1	cytochrome P450, family 19, subfamily A, polypeptide 1	MR	0.743	**0.000**	0.408	0.627	0.120	0.219	0.652	1.56	2.42	2.65	4.42	1.23	1.43	3.02	3.84	1.33	2.00	3.43	5.08
Dnmt1	DNA (cytosine-5-)-methyltransferase 1	MR	0.979	**0.003**	0.785	0.198	0.696	0.084	**0.002**	1.48	1.50	1.56	1.87	1.77	1.25	1.63	1.94	2.08	1.14	1.87	1.91
Dnmt3a	DNA (cytosine-5-)-methyltransferase 3a	MR	0.110	**0.000**	0.814	0.117	0.699	0.608	0.278	7.69	2.00	1.51	1.47	8.70	1.57	1.49	1.51	11.72	1.44	1.81	1.59
Esr1	estrogen receptor 1	MR	0.726	**0.000**	0.284	0.600	0.191	0.053	0.530	2.34	4.80	4.41	5.72	1.11	3.28	4.37	4.74	1.27	3.85	4.84	5.57
Esr2	estrogen receptor 2	MR	0.067	**0.000**	0.922	0.461	0.084	0.178	0.094	1.72	2.40	2.63	3.96	1.44	1.66	2.46	3.22	1.10	1.87	3.08	3.93
Gapdh	glyceraldehyde-3-phosphate dehydrogenase	MR	0.438	**0.000**	0.985	0.457	0.694	0.501	0.029	1.27	2.04	1.78	2.28	1.51	1.60	1.65	2.34	1.75	1.30	2.22	2.16
Gper	G protein-coupled estrogen receptor 1	MR	0.828	0.120	0.927	0.199	0.540	**0.003**	0.027	1.43	1.29	1.35	1.32	1.30	1.25	1.47	1.31	1.48	1.21	1.52	1.37
Gria1	glutamate receptor, ionotropic, AMPA 1	MR	0.417	**0.000**	0.909	0.084	0.216	0.580	0.212	1.37	1.50	1.51	2.03	1.34	1.20	1.44	1.79	1.58	1.21	1.73	1.87
Grin1	glutamate receptor, ionotropic, N-methyl D-aspartate 1	MR	0.569	**0.023**	0.471	0.199	0.431	0.437	**0.011**	1.26	1.44	1.27	1.82	1.50	1.19	1.39	1.56	1.60	1.11	1.55	1.66
Grin2b	glutamate receptor, ionotropic, N-methyl D-aspartate 2B	MR	0.622	**0.000**	0.546	0.290	0.684	0.817	0.075	1.57	1.24	1.60	2.17	1.98	1.39	1.37	1.66	2.20	1.09	1.71	2.13
Grin2c	glutamate receptor, ionotropic, N-methyl D-aspartate 2C	MR	0.410	**0.000**	0.460	0.068	0.727	0.721	0.085	1.05	1.84	1.95	2.25	1.29	1.38	1.79	2.30	1.29	1.26	2.02	2.01
Grin2d	glutamate receptor, ionotropic, N-methyl D-aspartate 2D	MR	0.260	**0.000**	0.749	0.189	0.798	0.611	**0.017**	1.99	1.70	1.66	2.05	2.46	1.62	1.60	1.81	2.62	1.09	1.81	1.90
Igf1r	insulin-like growth factor 1 receptor	MR	0.345	**0.000**	0.857	0.353	0.382	0.113	**0.031**	1.08	1.42	1.40	1.84	1.07	1.26	1.50	1.62	1.35	1.14	1.56	1.81
Kiss1r	KISS1 receptor	MR	0.148	**0.000**	0.755	0.626	0.587	0.133	**0.006**	1.52	1.97	2.33	2.94	1.54	1.63	2.27	2.77	1.51	1.58	2.78	2.77
Mc3r	melanocortin 3 receptor	MR	0.282	**0.000**	0.839	0.952	0.010	0.268	0.100	1.96	3.43	4.17	4.89	1.48	2.50	2.63	3.93	1.44	2.81	4.99	5.47
Mc4r	melanocortin 4 receptor	MR	0.096	**0.000**	0.457	0.141	0.657	0.731	0.168	1.24	1.96	1.92	2.60	1.64	1.75	1.75	2.49	1.61	1.62	2.95	3.37
Oxtr	oxytocin receptor	MR	0.922	**0.000**	0.961	0.298	0.801	0.224	0.241	2.55	1.49	1.43	2.03	2.05	1.27	1.40	1.71	2.52	0.96	1.85	1.89
Pdyn	prodynorphin	MR	0.197	**0.000**	0.402	0.495	0.012	0.121	0.056	1.56	1.96	2.58	3.21	1.11	1.34	1.93	2.51	1.33	1.83	3.35	2.75
Per2	period homolog 2	MR	0.248	**0.000**	0.636	0.913	0.006	0.448	**0.006**	1.17	2.18	2.28	3.32	1.28	1.68	2.29	2.37	1.35	1.79	2.69	2.75
Pgr	progesterone receptor	MR	0.805	**0.000**	0.357	0.420	0.145	0.531	0.579	1.52	2.12	3.15	4.29	1.39	1.66	2.95	3.78	1.41	1.71	3.71	4.49
Slc17a6	solute carrier family 17, member 6	MR	0.378	**0.000**	0.253	0.895	0.010	0.101	0.126	1.27	1.58	1.47	1.90	1.14	1.14	1.41	1.60	1.22	1.28	1.89	1.81
Srd5a1	steroid-5-alpha-reductase, alpha polypeptide 2	MR	0.897	**0.000**	0.233	0.102	0.539	0.473	0.067	1.20	1.67	1.60	1.83	1.37	1.50	1.86	2.09	1.32	1.17	1.77	1.68
Tgfa	transforming growth factor, alpha	MR	0.889	**0.000**	0.969	0.553	0.272	0.649	**0.007**	1.28	1.24	1.50	1.86	1.40	1.13	1.34	1.75	1.53	1.02	1.83	1.77
Tgfb1	transforming growth factor, beta 1	MR	0.979	0.068	0.410	0.244	0.763	0.708	0.098	1.70	1.63	1.41	1.69	1.88	1.30	1.45	1.87	1.95	1.26	1.73	1.67
Thra	thyroid hormone receptor, alpha	MR	0.835	0.087	0.728	0.124	0.162	0.419	**0.001**	1.28	1.78	1.51	2.11	1.55	1.20	1.51	1.72	1.57	1.14	1.91	1.76
Thrb	thyroid hormone receptor, beta	MR	0.353	**0.000**	0.980	0.242	0.555	0.344	0.103	1.16	1.97	1.96	2.34	1.41	1.49	1.82	2.42	1.37	1.36	2.23	2.62
			Males-Statistical Results (NP)							**Male - DMSO**				**Male - EB**				**Male - A1221**			
Ahr	aryl hydrocarbon receptor	NP	0.410	**0.000**	0.432	**0.000**	0.693	**0.000**	**0.000**	3.35	1.79	1.62	1.70	3.70	1.83	1.96	1.93	4.92	1.58	1.75	1.42
Avp	arginine vasopressin	NP	0.743	**0.000**	0.353	**0.002**	0.420	**0.002**	**0.015**	1.38	4.71	3.36	3.28	0.96	2.80	3.05	7.03	1.20	3.13	2.23	3.81
Gad1	glutamate decarboxylase 1 (brain, 67kDa)	NP	0.634	0.346	0.988	0.256	0.923	0.485	0.130	1.22	1.49	1.38	1.53	1.52	1.50	1.50	1.93	1.68	1.22	1.46	1.64
Gad2	glutamate decarboxylase 2 (pancreatic islets and brain, 65kDa)	NP	0.437	**0.037**	0.936	0.057	0.913	0.104	0.030	1.29	1.40	1.23	1.60	1.53	1.30	1.39	1.62	1.69	1.08	1.51	1.64
Gal	galanin prepropeptide	NP	0.995	**0.000**	0.799	**0.000**	0.308	**0.000**	**0.000**	1.78	4.08	4.74	7.08	1.41	2.61	4.17	6.11	1.51	2.92	6.74	6.28
Gnrh1	gonadotropin-releasing hormone 1	NP	0.790	**0.000**	0.944	**0.000**	0.711	**0.000**	**0.000**	1.55	3.68	4.37	4.28	1.64	2.26	3.71	4.49	1.40	2.36	4.75	4.06
Gria2	glutamate receptor, ionotropic, AMPA 2	NP	0.938	0.079	0.856	0.112	0.832	0.375	0.057	1.39	1.18	1.25	1.59	1.44	1.11	1.17	1.36	1.42	1.04	1.34	1.37
Grik2	glutamate receptor, ionotropic, kainate 2	NP	0.942	**0.003**	0.630	**0.002**	0.808	0.081	**0.019**	1.49	1.31	1.17	1.40	1.82	1.12	1.15	1.25	1.65	1.20	1.33	1.31
Grin2a	glutamate receptor, ionotropic, N-methyl D-aspartate 2A	NP	0.484	0.323	0.697	0.509	0.559	0.790	0.553	1.19	1.44	1.29	1.88	1.42	1.29	1.36	1.49	1.70	1.16	1.62	1.71
Igf1	insulin-like growth factor 1	NP	0.016	**0.000**	0.617	**0.000**	0.227	**0.000**	**0.000**	2.01	1.29	1.30	1.38	2.73	1.14	1.24	1.41	3.21	1.06	1.20	1.16
Kiss1	KiSS-1 metastasis-suppressor	NP	**0.000**	**0.000**	0.266	**0.000**	**0.001**	**0.000**	**0.000**	2.45	2.30	8.97	13.33	2.25	1.08	8.14	13.62	2.07	1.29	14.42	9.57
Lepr	leptin receptor	NP	0.431	**0.000**	0.846	**0.000**	0.943	**0.000**	**0.000**	1.49	2.03	2.85	3.79	1.44	1.61	2.80	4.40	1.29	2.16	3.44	3.37
Oxt	oxytocin, prepropeptide	NP	0.900	**0.000**	0.730	**0.000**	0.644	0.000	**0.000**	2.85	8.88	18.23	13.40	1.51	8.30	11.98	15.56	0.99	9.60	13.46	20.15
Tac2	tachykinin 2	NP	0.100	**0.000**	0.903	**0.000**	0.605	**0.002**	**0.006**	1.18	1.41	1.61	1.98	1.55	1.20	1.49	1.71	1.74	1.33	2.15	1.87
Dnmt3l	DNA (cytosine-5-)-methyltransferase 3l	N/A																			
Gnrhr	gonadotropin-releasing hormone receptor	N/A																			
Mc5r	melanocortin5 receptor	N/A																			

Results of 48-gene qPCR low-density arrays are shown. Gene expression data are mean.

Statistical results are based on multiple regression analysis (MR) or non-parametric tests (NP). Genes that did not amplify are indicated by N/A.

Significant p-values are shown in bold text.

Supplemental Table 2. Expression of 48 genes in the ARC.

Females			Females-Statistical Results (MR)							Female - DMSO				Female - EB				Female - A1221			
Gene Symbol	Gene Name	Statistic	Sex	Age	Trt	Sex X Age	Sex X Trt	Age X Trt	Sex X Age X Trt	P15	P30	P45	P90	P15	P30	P45	P90	P15	P30	P45	P90
18s	Eukaryotic 18S RNA, 18S ribosomal 1	MR	0.785	0.262	0.616	0.462	0.961	0.776	0.136	1.14	1.31	1.35	1.25	1.39	1.27	1.46	1.20	1.27	1.33	1.27	1.24
Ahr	aryl hydrocarbon receptor	MR	0.467	**0.000**	0.353	0.252	0.056	0.951	0.991	2.45	1.72	1.26	1.30	2.27	1.35	1.26	1.69	3.02	1.83	1.62	2.08
Ar	androgen receptor	MR	0.987	**0.000**	0.996	0.460	0.163	0.817	0.033	1.32	2.19	2.46	1.89	1.28	1.71	2.01	2.37	1.49	2.28	1.93	2.17
Arntl	aryl hydrocarbon receptor nuclear translocator-like	MR	0.824	0.155	0.654	0.928	0.347	0.728	0.865	1.42	1.54	1.43	1.46	1.39	1.34	1.25	1.84	1.64	1.52	1.44	1.66
Avpr1a	arginine vasopressin receptor 1A	MR	0.149	**0.000**	0.697	0.465	0.174	0.361	0.459	2.74	2.04	1.67	1.25	1.88	1.37	1.45	1.68	2.20	1.91	1.84	1.70
Bdnf	brain-derived neurotrophic factor	MR	0.578	**0.000**	0.981	0.960	0.341	0.513	0.412	3.48	1.60	1.97	1.69	3.63	1.79	1.58	1.42	3.53	2.07	1.71	1.32
Dnmt1	DNA (cytosine-5-)-methyltransferase 1	MR	0.265	0.014	0.856	0.686	0.160	0.853	0.289	2.19	1.86	1.91	1.53	2.01	1.49	1.31	2.16	2.26	1.91	1.71	1.98
Esr1	estrogen receptor 1	MR	0.942	**0.000**	0.848	0.071	0.300	0.932	0.549	1.60	1.88	2.12	2.35	1.36	1.69	1.76	2.43	1.42	1.95	2.08	2.78
Esr2	estrogen receptor 2	MR	0.707	**0.000**	0.356	0.500	0.080	0.731	0.611	1.32	1.68	2.12	2.75	1.18	1.17	1.89	3.88	1.34	1.55	2.21	3.00
Gad1	glutamate decarboxylase 1 (brain, 67kDa)	MR	0.317	0.064	0.224	0.486	0.137	0.950	0.083	1.57	1.65	1.83	1.66	1.72	1.74	1.44	2.42	1.92	1.79	1.87	2.25
Gad2	glutamate decarboxylase 2 (pancreatic islets and brain, 65kDa)	MR	0.731	**0.001**	0.765	0.767	0.194	0.826	0.157	2.74	2.25	2.12	1.81	2.41	1.96	1.82	2.35	2.77	2.33	2.13	2.26
Gal	galanin prepropeptide	MR	0.760	**0.000**	0.189	0.861	0.258	0.883	0.761	1.38	3.33	4.71	4.79	1.61	3.10	3.68	6.06	2.03	2.37	3.52	4.41
Gapdh	glyceraldehyde-3-phosphate dehydrogenase	MR	0.357	0.160	0.955	0.763	0.731	0.868	0.502	1.36	1.77	1.81	1.50	1.28	1.30	1.81	2.01	1.59	1.59	1.52	1.76
Gnrh1	gonadotropin-releasing hormone 1	MR	0.104	0.115	0.280	0.242	0.735	1.000	0.313	1.61	1.61	2.30	2.26	1.12	1.37	2.24	2.34	1.84	1.64	1.61	2.12
Gria1	glutamate receptor, ionotropic, AMPA 1	MR	0.480	0.867	0.769	0.763	0.210	0.874	0.109	1.50	1.72	1.97	1.48	1.58	1.52	1.41	1.79	1.80	1.82	1.65	1.58
Gria2	glutamate receptor, ionotropic, AMPA 2	MR	0.775	**0.000**	0.701	0.397	0.705	0.711	0.134	1.81	1.76	1.61	1.25	1.76	1.42	1.16	1.47	1.78	1.70	1.38	1.34
Grik2	glutamate receptor, ionotropic, kainate 2	MR	0.689	**0.003**	0.690	0.604	0.202	0.896	0.018	1.65	1.32	1.61	1.17	1.42	1.29	1.05	1.41	1.78	1.51	1.33	1.35
Grin1	glutamate receptor, ionotropic, N-methyl D-aspartate 1	MR	0.736	**0.000**	0.928	0.420	0.037	0.895	0.200	1.61	1.41	1.33	1.07	1.53	1.30	1.06	1.33	1.82	1.57	1.31	1.33
Grin2a	glutamate receptor, ionotropic, N-methyl D-aspartate 2A	MR	0.932	0.341	0.808	0.890	0.096	0.774	0.238	1.64	1.43	1.54	1.19	1.47	1.35	1.07	1.36	1.63	1.47	1.47	1.43
Grin2b	glutamate receptor, ionotropic, N-methyl D-aspartate 2B	MR	0.926	**0.000**	0.604	0.764	0.447	0.778	0.299	2.20	1.73	1.65	1.56	2.34	1.36	1.62	1.77	2.24	1.77	1.60	1.62
Grin2c	glutamate receptor, ionotropic, N-methyl D-aspartate 2C	MR	0.968	**0.000**	0.739	0.715	0.349	0.816	0.226	1.15	2.77	3.75	3.00	1.41	2.57	3.05	3.04	1.22	2.72	2.71	3.31
Grin2d	glutamate receptor, ionotropic, N-methyl D-aspartate 2D	MR	0.587	**0.000**	0.075	0.467	0.004	0.349	0.138	3.05	1.74	1.70	1.54	3.05	1.75	1.23	1.84	3.28	1.95	1.85	1.73
Igf1	insulin-like growth factor 1	MR	0.974	0.085	0.417	0.919	0.559	0.960	0.819	1.98	1.45	1.65	1.61	1.86	1.59	1.72	1.77	1.73	1.68	1.50	2.12
Igf1r	insulin-like growth factor 1 receptor	MR	0.872	**0.003**	0.569	0.896	0.116	0.676	0.613	1.43	1.57	1.42	1.48	1.12	1.37	1.46	1.91	1.49	1.70	1.47	2.07
Kiss1	KiSS-1 metastasis-suppressor	MR	**0.000**	**0.000**	0.337	0.276	0.592	0.971	0.729	3.58	4.77	13.74	10.34	2.87	3.86	8.12	13.17	3.14	4.04	8.14	8.45
Kiss1r	KISS1 receptor	MR	0.086	**0.000**	0.635	0.577	0.130	0.944	0.689	1.41	1.98	2.33	3.20	1.34	1.67	1.88	3.91	1.42	1.61	2.62	3.45
Lepr	leptin receptor	MR	0.821	**0.000**	0.616	0.495	0.207	0.642	0.030	1.74	2.00	2.28	2.24	1.04	1.85	1.84	2.90	1.61	2.46	2.30	2.76
Mc3r	melanocortin 3 receptor	MR	0.824	0.277	0.413	0.408	0.006	0.808	0.410	1.59	1.98	1.76	1.30	1.22	1.24	1.38	1.24	1.41	1.75	1.50	1.27
Oxt	oxytocin, prepropeptide	MR	0.459	**0.000**	0.335	0.025	0.046	0.396	0.200	1.38	5.99	11.88	7.49	1.36	3.60	6.69	17.80	2.79	7.94	10.72	15.89
Per2	period homolog 2	MR	0.949	0.016	0.710	0.389	0.070	0.896	0.569	1.90	1.86	1.97	2.22	1.64	1.71	1.61	2.35	1.83	1.99	2.02	2.84
Pgr	progesterone receptor	MR	**0.000**	**0.000**	0.193	0.087	0.186	0.939	0.186	1.49	1.66	4.88	3.88	1.37	1.56	3.25	5.07	1.42	1.73	3.86	3.90
Slc17a6	solute carrier family 17, member 6	MR	0.435	0.003	0.508	0.768	0.222	0.504	0.106	2.35	2.01	2.26	1.66	2.29	1.79	1.41	1.61	2.35	2.18	1.83	1.56
Srd5a1	steroid-5-alpha-reductase, alpha polypeptide 2	MR	0.217	0.133	0.473	0.195	0.437	0.748	0.885	1.87	2.00	1.79	1.79	2.02	1.85	1.62	2.22	2.15	2.17	1.82	1.90
Tac2	tachykinin 2	MR	**0.000**	**0.000**	0.458	0.006	0.666	0.860	0.322	2.62	3.90	10.28	10.29	2.24	3.43	6.52	13.72	2.59	3.35	8.86	7.92
Tgfa	transforming growth factor, alpha	MR	0.224	**0.000**	0.602	0.449	0.490	0.431	0.578	1.66	1.67	1.45	1.79	1.63	1.33	1.33	2.50	1.93	1.50	1.64	1.99
Tgfb1	transforming growth factor, beta 1	MR	0.594	0.004	0.639	0.828	0.101	0.549	0.927	1.82	1.62	1.48	1.66	1.72	1.30	1.32	2.17	2.18	1.59	1.88	2.13
Thra	thyroid hormone receptor, alpha	MR	0.510	0.286	0.922	0.836	0.247	0.882	0.471	1.68	1.68	1.61	1.30	1.59	1.37	1.18	1.68	1.87	1.72	1.53	1.43
Thrb	thyroid hormone receptor, beta	MR	0.966	**0.000**	0.889	0.406	0.090	0.919	0.428	1.43	2.89	3.08	2.71	1.45	2.29	2.27	4.01	1.63	2.69	2.81	4.30
			Females-Statistical Results (NP)							Female - DMSO				Female - EB				Female - A1221			
Avp	arginine vasopressin	NP	0.050	0.023	0.447	**0.000**	0.267	0.049	**0.000**	10.89	7.99	3.48	1.57	2.15	12.87	2.38	3.43	3.91	6.40	1.99	2.27
Cyp19a1	cytochrome P450, family 19, subfamily A, polypeptide 1	NP	0.212	**0.001**	0.592	**0.004**	0.359	0.031	0.012	1.14	1.60	1.99	1.57	1.47	1.11	1.79	1.80	1.28	1.89	1.49	1.53
Dnmt3a	DNA (cytosine-5-)-methyltransferase 3a	NP	0.802	**0.000**	0.994	**0.000**	0.995	**0.000**	**0.000**	6.49	1.78	1.25	1.18	5.76	1.36	1.54	1.72	5.61	1.50	1.54	1.54
Gnrhr	gonadotropin-releasing hormone receptor	NP	0.15	0.035	0.109	**0.002**	0.214	0.109	0.03	0.64	0.93	1.60	1.54	0.53	0.71	1.13	3.94	0.55	1.09	1.57	0.94
Gper	G protein-coupled estrogen receptor 1	NP	0.611	0.001	0.560	0.011	0.517	0.051	0.159	2.38	1.60	1.56	1.11	2.19	1.56	1.63	1.43	2.17	1.87	1.69	1.59
Mc4r	melanocortin 4 receptor	NP	0.092	0.034	0.802	0.074	0.622	0.065	0.223	1.57	1.36	1.85	1.55	1.68	1.78	1.36	1.56	2.56	1.67	0.91	1.67
Oxtr	oxytocin receptor	NP	0.086	**0.000**	0.558	**0.000**	0.282	**0.005**	0.009	1.67	1.82	3.14	3.45	1.63	1.57	3.38	3.23	1.76	2.15	3.16	3.01
Pdyn	prodynorphin	NP	0.085	0.182	0.517	0.216	0.129	0.386	0.107	2.53	3.44	3.26	2.08	2.35	1.96	3.12	2.41	2.52	3.20	2.73	2.02
Dnmt3l	DNA (cytosine-5-)-methyltransferase 3l	N/A	0.176	0.102	0.74	0.94	0.539	0.421	0.49												
Mc5r	melanocortin5 receptor	N/A	0.738	0.473	0.333	0.239	0.848	0.708	0.785												

Males			Males-Statistical Results (MR)							Male - DMSO				Male - EB				Male - A1221			
Gene Symbol	Gene Name	Statistic	Sex	Age	Trt	Sex X Age	Sex X Trt	Age X Trt	Sex X Age X Trt	P15	P30	P45	P90	P15	P30	P45	P90	P15	P30	P45	P90
18s	Eukaryotic 18S RNA, 18S ribosomal 1	MR	0.785	0.262	0.616	0.462	0.961	0.776	0.136	1.37	1.24	1.42	1.05	1.32	1.55	1.05	1.30	1.26	1.35	1.24	1.18
Ahr	aryl hydrocarbon receptor	MR	0.467	**0.000**	0.353	0.252	0.056	0.951	0.991	2.20	1.51	1.62	1.65	2.96	1.57	1.79	2.48	2.43	1.30	1.43	2.02
Ar	androgen receptor	MR	0.987	**0.000**	0.996	0.460	0.163	0.817	0.033	1.34	2.16	1.56	2.85	1.41	2.09	2.53	2.33	1.32	1.40	2.54	1.99
Arntl	aryl hydrocarbon receptor nuclear translocator-like	MR	0.824	0.155	0.654	0.928	0.347	0.728	0.865	1.41	1.42	1.14	1.64	1.60	1.52	1.49	1.82	1.60	1.13	1.50	1.42
Avpr1a	arginine vasopressin receptor 1A	MR	0.149	**0.000**	0.697	0.465	0.174	0.361	0.459	2.61	1.59	1.60	1.87	2.34	1.92	2.08	1.87	2.54	1.37	2.13	1.72
Bdnf	brain-derived neurotrophic factor	MR	0.578	**0.000**	0.981	0.960	0.341	0.513	0.412	3.77	1.74	1.07	1.73	3.39	2.13	1.91	1.79	3.11	1.21	2.01	1.23
Dnmt1	DNA (cytosine-5-)-methyltransferase 1	MR	0.265	0.014	0.856	0.686	0.160	0.853	0.289	2.43	1.86	1.37	2.15	2.50	1.68	2.53	2.20	2.21	1.36	1.93	1.87
Esr1	estrogen receptor 1	MR	0.942	**0.000**	0.848	0.071	0.300	0.932	0.549	1.08	2.11	2.09	2.93	1.47	1.53	3.14	2.68	1.11	1.23	2.75	2.56
Esr2	estrogen receptor 2	MR	0.707	**0.000**	0.356	0.500	0.080	0.731	0.611	1.04	1.46	2.16	3.24	1.35	1.61	2.77	3.88	1.06	0.96	2.35	2.89
Gad1	glutamate decarboxylase 1 (brain, 67kDa)	MR	0.317	0.064	0.224	0.486	0.137	0.950	0.083	1.75	1.79	1.57	2.28	2.02	1.91	2.68	2.04	1.84	1.33	2.02	1.93
Gad2	glutamate decarboxylase 2 (pancreatic islets and brain, 65kDa)	MR	0.731	**0.001**	0.765	0.767	0.194	0.826	0.157	2.48	2.06	1.69	2.49	3.05	2.54	2.39	2.05	3.09	1.47	2.30	1.87
Gal	galanin prepropeptide	MR	0.760	**0.000**	0.189	0.861	0.258	0.883	0.761	1.32	3.35	3.25	4.70	1.80	4.95	4.96	5.69	1.15	2.10	3.60	4.69
Gapdh	glyceraldehyde-3-phosphate dehydrogenase	MR	0.357	0.160	0.955	0.763	0.731	0.868	0.502	1.42	1.68	1.34	2.05	1.43	1.80	1.93	2.08	1.51	1.35	1.78	1.78
Gnrh1	gonadotropin-releasing hormone 1	MR	0.104	0.115	0.280	0.242	0.735	1.000	0.313	2.00	1.70	1.78	1.81	1.97	1.26	1.43	1.49	1.22	1.01	1.99	1.30
Gria1	glutamate receptor, ionotropic, AMPA 1	MR	0.480	0.867	0.769	0.763	0.210	0.874	0.109	1.74	1.58	1.31	1.90	1.68	1.52	1.91	1.66	1.43	1.25	1.82	1.24
Gria2	glutamate receptor, ionotropic, AMPA 2	MR	0.775	**0.000**	0.701	0.397	0.705	0.711	0.134	1.97	1.52	1.12	1.63	1.80	1.42	1.58	1.43	2.03	1.34	1.69	1.17
Grik2	glutamate receptor, ionotropic, kainate 2	MR	0.689	**0.003**	0.690	0.604	0.202	0.896	0.018	1.65	1.41	1.07	1.68	1.72	1.27	1.45	1.43	1.56	1.13	1.57	1.27
Grin1	glutamate receptor, ionotropic, N-methyl D-aspartate 1	MR	0.736	**0.000**	0.928	0.420	0.037	0.895	0.200	1.84	1.41	1.01	1.50	1.84	1.28	1.70	1.34	1.53	1.00	1.41	1.12
Grin2a	glutamate receptor, ionotropic, N-methyl D-aspartate 2A	MR	0.932	0.341	0.808	0.890	0.096	0.774	0.238	1.62	1.44	1.01	1.76	1.63	1.55	1.57	1.48	1.41	1.02	1.55	1.08
Grin2b	glutamate receptor, ionotropic, N-methyl D-aspartate 2B	MR	0.926	**0.000**	0.604	0.764	0.447	0.778	0.299	2.19	1.54	1.36	2.14	2.31	1.82	2.03	1.61	1.92	1.26	1.93	1.47
Grin2c	glutamate receptor, ionotropic, N-methyl D-aspartate 2C	MR	0.968	**0.000**	0.739	0.715	0.349	0.816	0.226	1.32	2.79	2.53	3.52	1.45	2.95	3.85	2.70	1.40	2.08	2.90	2.46
Grin2d	glutamate receptor, ionotropic, N-methyl D-aspartate 2D	MR	0.587	**0.000**	0.075	0.467	0.004	0.349	0.138	2.72	1.72	1.33	1.85	4.49	2.15	2.12	1.60	3.22	1.20	1.71	1.36
Igf1	insulin-like growth factor 1	MR	0.974	0.085	0.417	0.919	0.559	0.960	0.819	1.75	1.53	1.17	1.81	2.09	1.82	1.76	2.05	1.95	1.11	1.62	1.94
Igf1r	insulin-like growth factor 1 receptor	MR	0.872	**0.003**	0.569	0.896	0.116	0.676	0.613	1.29	1.59	1.22	1.85	1.41	1.66	1.79	2.03	1.37	1.09	1.64	1.73
Kiss1	KiSS-1 metastasis-suppressor	MR	**0.000**	**0.000**	0.337	0.276	0.592	0.971	0.729	1.77	2.15	5.75	5.13	2.02	2.18	9.88	6.14	1.63	1.75	6.85	4.89
Kiss1r	KISS1 receptor	MR	0.086	**0.000**	0.635	0.577	0.130	0.944	0.689	1.26	2.02	2.75	4.53	1.46	2.42	3.81	4.92	1.45	1.62	2.49	3.40
Lepr	leptin receptor	MR	0.821	**0.000**	0.616	0.495	0.207	0.642	0.030	1.33	2.22	1.93	3.40	1.50	1.58	2.79	2.60	1.32	1.83	2.52	2.33
Mc3r	melanocortin 3 receptor	MR	0.824	0.277	0.413	0.408	0.006	0.808	0.410	1.43	1.33	1.19	1.58	1.59	1.70	1.92	1.63	1.09	1.04	1.82	1.03
Oxt	oxytocin, prepropeptide	MR	0.459	**0.000**	0.335	0.025	0.046	0.396	0.200	3.13	5.31	4.13	10.64	3.93	6.74	12.22	21.56	4.14	2.20	4.28	14.66
Per2	period homolog 2	MR	0.949	0.016	0.710	0.389	0.070	0.896	0.569	1.96	1.63	1.54	2.22	1.95	1.85	2.77	2.59	2.27	1.14	1.93	1.97
Pgr	progesterone receptor	MR	**0.000**	**0.000**	0.193	0.087	0.186	0.939	0.186	1.48	1.43	1.98	2.94	1.66	1.47	3.18	3.21	1.21	0.98	2.60	2.55
Slc17a6	solute carrier family 17, member 6	MR	0.435	0.003	0.508	0.768	0.222	0.504	0.106	2.48	1.82	1.30	2.03	2.28	1.89	1.86	1.80	1.73	1.53	2.24	1.25
Srd5a1	steroid-5-alpha-reductase, alpha polypeptide 2	MR	0.217	0.133	0.473	0.195	0.437	0.748	0.885	2.01	1.73	1.58	2.62	2.31	1.95	2.12	2.90	2.14	1.54	2.23	2.04
Tac2	tachykinin 2	MR	**0.000**	**0.000**	0.458	0.006	0.666	0.860	0.322	2.05	1.46	3.03	4.92	2.02	1.52	5.78	5.50	2.23	1.28	2.61	4.70
Tgfa	transforming growth factor, alpha	MR	0.224	**0.000**	0.602	0.449	0.490	0.431	0.578	1.85	1.48	1.36	2.47	1.89	1.47	2.24	2.45	1.99	1.05	1.89	2.00
Tgfb1	transforming growth factor, beta 1	MR	0.594	0.004	0.639	0.828	0.101	0.549	0.927	1.80	1.62	1.38	2.16	1.92	1.61	2.04	2.43	1.92	1.09	1.85	1.85
Thra	thyroid hormone receptor, alpha	MR	0.510	0.286	0.922	0.836	0.247	0.882	0.471	1.95	1.62	1.14	1.83	1.83	1.61	1.92	1.71	1.75	1.23	1.60	1.34
Thrb	thyroid hormone receptor, beta	MR	0.966	**0.000**	0.889	0.406	0.090	0.919	0.428	1.39	2.86	2.61	3.90	1.56	2.61	3.83	4.14	1.19	1.97	3.26	3.28
			Males-Statistical Results (NP)							Male - DMSO				Male - EB				Male - A1221			
Avp	arginine vasopressin	NP	0.050	0.023	0.447	**0.000**	0.267	0.049	**0.000**	19.81	5.59	2.85	5.64	8.78	2.30	3.97	6.03	32.00	1.23	2.81	4.17
Cyp19a1	cytochrome P450, family 19, subfamily A, polypeptide 1	NP	0.212	**0.001**	0.592	**0.004**	0.359	0.031	0.012	1.43	1.67	1.58	2.57	1.49	1.93	1.68	2.13	1.05	1.12	2.28	1.78
Dnmt3a	DNA (cytosine-5-)-methyltransferase 3a	NP	0.802	**0.000**	0.994	**0.000**	0.995	**0.000**	**0.000**	5.98	1.63	1.26	1.56	6.45	1.73	1.38	1.73	6.67	1.18	1.63	1.49
Gnrhr	gonadotropin-releasing hormone receptor	NP	0.15	0.035	0.109	**0.002**	0.214	0.109	0.03	2.03	1.20	1.60	1.13	2.02	1.03	1.66	1.61	1.43	0.64	0.97	1.86
Gper	G protein-coupled estrogen receptor 1	NP	0.611	0.001	0.560	0.011	0.517	0.051	0.159	1.99	1.85	1.30	1.59	2.32	2.01	2.15	1.54	2.01	1.36	2.04	1.30
Mc4r	melanocortin 4 receptor	NP	0.092	0.034	0.802	0.074	0.622	0.065	0.223	1.58	1.42	1.62	2.17	2.85	2.54	1.66	1.97	2.60	1.35	1.75	2.39
Oxtr	oxytocin receptor	NP	0.086	**0.000**	0.558	**0.000**	0.282	**0.005**	0.009	1.89	1.86	1.48	3.17	2.06	1.55	2.94	2.93	1.82	1.10	2.40	1.75
Pdyn	prodynorphin	NP	0.085	0.182	0.517	0.216	0.129	0.386	0.107	3.42	2.17	1.64	2.25	2.85	2.83	2.83	2.39	1.90	1.78	2.62	1.45
Dnmt3l	DNA (cytosine-5-)-methyltransferase 3l	N/A	0.176	0.102	0.74	0.94	0.539	0.421	0.49												
Mc5r	melanocortin5 receptor	N/A	0.738	0.473	0.333	0.239	0.848	0.708	0.785												

Results of 48-gene qPCR low-density arrays are shown. Gene expression data are mean.

Statistical results are based on multiple regression analysis (MR) or non-parametric tests (NP). Genes that did not amplify are indicated by N/A.

Significant p-values are shown in bold text.