Functional Genomic Architecture of Predisposition to Voluntary Exercise in Mice: Expression QTL in the Brain

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ABSTRACT The biological basis of voluntary exercise is complex and simultaneously controlled by peripheral (ability) and central (motivation) mechanisms. The accompanying natural reward, potential addiction, and the motivation associated with exercise are hypothesized to be regulated by multiple brain regions, neurotransmitters, peptides, and hormones. We generated a large (n = 815) advanced intercross line of mice (G_4) derived from a line selectively bred for increased wheel running (high runner) and the C57BL/6J inbred strain. We previously mapped multiple quantitative trait loci (QTL) that contribute to the biological control of voluntary exercise levels, body weight, and composition, as well as changes in body weight and composition in response to short-term exercise. Currently, using a subset of the G_4 population (n = 244), we examined the transcriptional landscape relevant to neurobiological aspects of voluntary exercise by means of global mRNA expression profiles from brain tissue. We identified genome-wide expression quantitative trait loci (eQTL) regulating variation in mRNA abundance and determined the mode of gene action and the *cis*- and/or *trans*-acting nature of each eQTL. Subsets of *cis*-acting eQTL, colocalizing with QTL for exercise or body composition traits, were used to identify candidate genes based on both positional and functional evidence, which were further filtered by correlational and exclusion mapping analyses. Specifically, we discuss six plausible candidate genes (*Insig2*, *Socs2*, *DBY*, *Arrdc4*, *Prcp*, *IL15*) and their potential role in the regulation of voluntary activity, body composition, and their interactions. These results develop a potential initial model of the underlying functional genomic architecture of predisposition to voluntary exercise and its effects on body weight and composition within a neurophysiological framework.

VOLUNTARY exercise levels are considerably variable in mice (*e.g.*, Lightfoot *et al.* 2004) and humans (*e.g.*, Centers for Disease Control and Prevention (CDC) 2003); may be an important predictor of human health-related quality of life (Booth *et al.* 2000; Friedenreich and Orenstein 2002); and are influenced by multiple environmental variables, genetic factors, and their interactions (review by Garland *et al.* 2011b). Furthermore, multiple lines of evidence suggest that the biological basis of voluntary exercise behavior is composed of both ability and motivation (Waters *et al.* 2008; Meek *et al.* 2009; reviewed in Knab and Lightfoot 2010; Garland *et al.* 2011b). These two components are almost certainly not mutually exclusive in their contribution to voluntary exercise, their relative influence may vary among individuals, and each undoubtedly has a genetic basis (Dishman 2008; Bray *et al.* 2009).

From a neurobiological perspective, exercise in humans and rodents is hypothesized to be self-rewarding (*e.g.*, Brené *et al.* 2007), potentially addictive (MacLaren and Best 2010), and a highly motivated behavior (Sherwin 1998). For example, Sherwin and Nicol (1996) demonstrated that mice are motivated to engage in wheel running, even when the cost of gaining access to a wheel is increased by requiring shallow water traverses. Not only are mice apparently willing to incur a cost to gain access to a running wheel, but also operant conditioning studies have demonstrated that both rats and mice are motivated to lever press for the opportunity to run (Belke 2006; Belke and Garland 2007). In addition, selective breeding for both elevated endurance

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capacity in rats and elevated wheel running in mice has resulted in alterations to neurobiological pathways that appear to delay the onset of exercise-induced fatigue (rats: Foley *et al.* 2006) and increase motivation for wheel-running behavior (mice: Rhodes *et al.* 2005). Although a detailed understanding of the neurobiology of exercise is still years away, potential mechanistic foundations include multiple brain regions encompassing interactions between neurotransmitters, peptides, and hormones (see figure 1 in Kotz *et al.* 2008; figure 5 in Garland *et al.* 2011b). More specifically, pharmacological experiments on mice selectively bred for elevated wheel running have implicated alterations in dopamine function (Rhodes *et al.* 2005; Knab and Lightfoot 2010; Mathes *et al.* 2010) and endocannabinoid signaling (Keeney *et al.* 2008) as underlying the neurobiology of high voluntary exercise.

In addition to voluntary exercise, dopamine and endocannabinoid signaling, among other central nervous system processes, have also been linked to aspects of eating behavior and obesity (Cagniard *et al.* 2006; Davis *et al.* 2008; Garland *et al.* 2011b). The interactions of these redundant neural systems are currently poorly understood (Lenard and Berthoud 2008), but it has been demonstrated in mice (Kumar *et al.* 2010) and humans (Cai *et al.* 2006) that food intake and physical activity, both components of energy balance, may be governed by a similar underlying genetic architecture. For example, Mathes *et al.* (2010) observed significant differential gene expression, with associated changes in the dopamine pathway (D1 and D2 receptors), G-proteins, and adenylate cyclase in mice selectively bred for either high running or obesity relative to a nonselected outbred strain of mice.

Previously, we generated an advanced intercross line (AIL; G_4) of mice that is broadly useful for investigation of the phenotypic relationships and genetic architecture of voluntary exercise behavior and related body composition traits. The AIL was created through reciprocal crosses between a line selectively bred for high voluntary wheel running and the inbred strain C57BL/6J (Kelly *et al.* 2010a). The use of an AIL (as opposed to an F_2 population) resulted in a threefold expansion of the genetic map (Kelly *et al.* 2010b) and led to increased QTL mapping resolution with reduced confidence intervals (C.I.'s) (Farber *et al.* 2011). The high-runner (HR) line utilized in creation of the AIL is a result of a replicated artificial selection experiment for increased voluntary wheel-running behavior on days 5 and 6 of a 6-day wheel exposure (Swallow *et al.* 1998). The HR lines have diverged significantly from the control lines with an ~2.5- to 3-fold increase in total revolutions/day with correlated changes in a number of morphological, physiological, and behavioral traits (reviewed in Swallow *et al.* 2009; Garland *et al.* 2011a).

Using this AIL, we have previously reported multiple QTL for voluntary exercise traits including daily wheel running (distance, duration, average speed, and maximum speed), running values averaged across days 5 and 6 of the 6-day test, and the running trajectory (slope and intercept) across the wheel-access period (Kelly *et al.* 2010b). We have also localized QTL controlling relationships between voluntary exercise, food consumption, and changes in body weight and composition (Kelly *et al.* 2011). In this report, as a complementary approach to further our understanding of the genetic architecture of exercise and its relationship with changes in body weight and composition, we examined global gene expression profiles in brain tissue. By combining QTL mapping with large-scale gene expression analysis, our primary goal was to further dissect these complex traits and make the selection of candidate genes underlying predisposition loci more efficient (*e.g.*, Pomp 2005). By initially using brain tissue, we attempted to capture the transcriptional landscape relevant to motivational aspects of voluntary exercise. Expression quantitative trait loci (eQTL) were identified, their additive and dominance gene action calculated, and the *cis*- and/or *trans*-acting nature determined. Subsets of *cis*-acting eQTL that mapped under loci for exercise or body composition traits were used to produce a list of potential candidate genes on the basis of their genomic position and/or known function. Combined with correlational and exclusion mapping analyses, these results begin to develop a more detailed description of the underlying genetic architecture of predisposition to voluntary exercise and its effects on body weight and composition within a neurophysiological framework.

Materials and Methods

Population and phenotyping

A G_4 population (n = 815) was generated from a reciprocal cross between mice selectively bred for high voluntary wheel running (HR line) and the inbred strain C57BL/6J (B6). Details regarding the creation and phenotyping of the G_4 population have been described elsewhere (Kelly *et al.* 2010a). Only methodological details relevant to the current suite of phenotypes and the corresponding statistical analyses will be described here. Details regarding the final set of SNPs utilized for the QTL analyses (n = 530), with an average genome-wide spacing of 4.7 Mb, have been provided elsewhere (Kelly *et al.* 2010b), and complete genotypes are provided in the Supporting Information, File S1.

G_4 mice at ~8 weeks of age were assessed for body weight and composition (percentage fat tissue and percentage lean tissue) (EchoMRI-100, Echo Medical Systems, Houston, TX) and then were individually housed with access to running wheels (circumference = 1.1 m) (Lafayette Instruments, Lafayette, IN; model 80850) for 6 sequential days. Voluntary running was recorded electronically at 1-min intervals for 23–24 hr daily. The following daily traits were calculated: distance (total revolutions), time spent running (cumulative 1-min intervals in which at least 1 revolution was recorded), average speed (total revolutions/time spent running), and maximum speed (highest number of revolutions in any 1-min interval within a 24-hr period).

In addition, we calculated mean values of the above traits on days 5 and 6 of the 6-day test, and the slope and intercept for regressions of distance, time, average speed, and maximum speed across the 6 days of wheel exposure. After body weight and composition measures were taken on day 6, mice were decapitated and brains were immediately harvested, placed on a chilled aluminum block, separated into left and right hemispheres, flash-frozen in liquid nitrogen, and stored at −80°. Percentage change in body mass in response to 6 days of voluntary wheel running was calculated as [(pre-wheel mass – post-wheel mass)/pre-wheel mass] × 100. Percentage change (after wheel access) in percentage body fat (and lean) was calculated as [(% post-wheel access – % pre-wheel access)/% pre-wheel access] × 100. All procedures were approved by and were conducted in accordance with the guidelines set forth by the Institutional Animal Care and Use Committee at the University of North Carolina at Chapel Hill.

RNA isolation and microarray analysis

Total RNA was isolated and purified from a homogenate of the right hemisphere of the brain from a subset of the G_4 population using TRIzol (Invitrogen, Carlsbad, CA). The subpopulation ($n = 244$) was utilized due to financial limitations in running microarrays and represented the population-wide variation in running distance. Among the subpopulation, each of two parent-of-origin types [whether a G_4 individual was descended from a progenitor (F_0) cross of HR♀ × B6♂ or B6♀ × HR♂] and sexes were equally represented, as these two factors have known effects on wheel-running behavior and body composition-related traits (see Kelly *et al.* 2010a). Within each of the four subpopulation categories, the 62 individuals were nonrandomly chosen to represent the entire distribution of running distance (*i.e.*, low, moderate, and high runners) observed across each subpopulation and across the full population. Four individuals were removed from the final analyses due to a lack of genotype information.

Following isolation and purification, RNA quality and quantity was determined by spectrophotometry (NanoDrop ND-1000, NanoDrop Technologies, Wilmington, DE) and bio-analysis (Genomics and Bioinformatics Core Facility, Lineberger Comprehensive Cancer Center, University of North Carolina School of Medicine, Chapel Hill, NC). Expression profiles were generated for 45,281 transcripts using the MouseWG-6 v2.0 Beadchip (Illumina, San Diego) and processed utilizing Microarray Services (Expression Analysis; Durham, NC). Following Gordon *et al.* (2010), transcript expression profiles were normalized using Loess-Quantile normalization methods with R v 2.8.1 statistical software (R Development Core Team, 2008; http://www.r-project.org, lumi package) (see File S2). Transcripts with a detection score ≥0.95 were considered to be expressed above background and utilized for correlation and eQTL (Burns *et al.* 2010; Gordon *et al.* 2010; O'Leary and Osborne 2011).

Correlation analysis

Phenotypic correlations were calculated using SAS (version 9.1, SAS Institute, Cary, NC) between all genes significantly expressed above background levels and exercise and body composition phenotypes previously measured in the G_4 population. In an attempt to determine if sex or parent-of-origin type were potentially underlying significant correlations with transcript levels, partial correlations were calculated adjusting for both factors (Kelly *et al.* 2010b, 2011). For all correlation analyses, adjustments for multiple comparisons were performed in SAS using the false-discovery-rate procedure controlling the overall type I error rate at 5% (Curran-Everett 2000).

eQTL analysis

eQTL were identified using the multiple imputation method (Sen and Churchill 2001) within R/qtl (Broman *et al.* 2003) for the R environment. Statistical models included effects of sex and parent of origin. Permutation ($n = 1000$) tests of 100 randomly selected transcripts yielded an average significance threshold of a log of the odds (LOD) > 3.8 (an approach similar to van Nas *et al.* 2010). This average threshold was calculated using R/qtl, which assumes an F_2 population structure and therefore independence among individuals. We acknowledge that our approach is only one of potentially many and that the threshold estimates may be imperfect in the context of available techniques. As new approaches that are more computationally efficient (*e.g.*, Zhang *et al.* 2012) and applicable to the current data set become available, thresholds computed here may be revisited.

Due to our more complex breeding history (G_4 as opposed to F_2), some adjustment of the LOD threshold is warranted (Valdar *et al.* 2009). The subpopulation utilized here ($n = 248$) was composed of 54 unique families with an average of four individuals representing each family (median = 4; minimum = 1; maximum = 11). For comparison, 57 unique families (average = 13 individuals per family; median = 13; minimum = 4; maximum = 28) were represented in the overall QTL mapping population ($n = 815$). Hence, we did not statistically account for family structure as in previous studies (see Kelly *et al.* 2010b, 2011). Rather, given the reduced population size, short number of intercrosses, and the relatively well-balanced mating design in our G_4, we chose the expedient approach of setting a higher LOD threshold; eQTL with LOD ratio scores >4.3 (P-value < 0.00005) were deemed significant (previously chosen by Schadt *et al.* 2003). In addition, we chose to highlight only candidate genes with high relative LOD scores or extensive existing functional support (as in the case of *arrestin domain containing 4*, or *Arrdc4*). We computed the distance of the mapped location of significant eQTL to the midpoint of the physical location of the gene that each represented. If the distance was ≤10 Mb, eQTL were classified as *cis*-acting or local eQTL. If the distance was >10 Mb (including on another chromosome), eQTL were classified as *trans*-acting

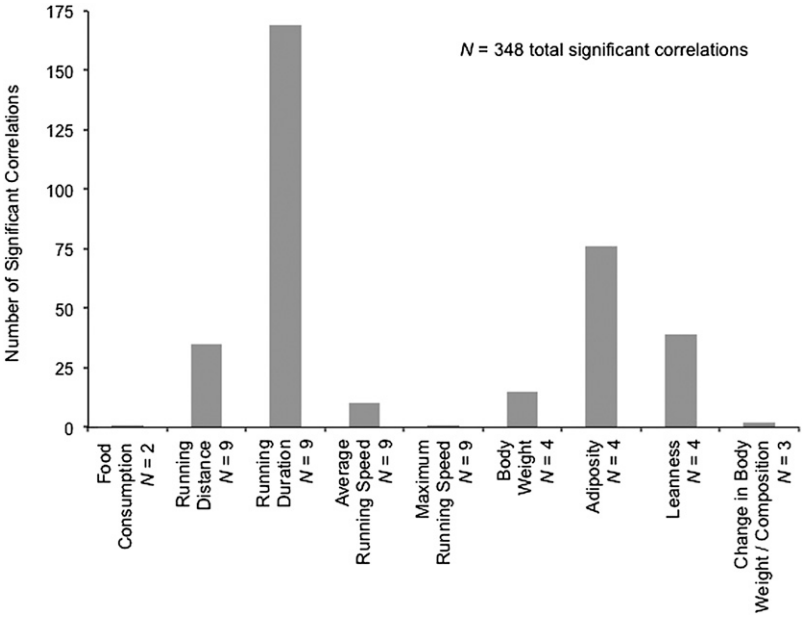

Figure 1 The number of statistically significant ($P \leq 0.05$, adjusted for multiple comparisons) partial correlations, adjusted for sex and parent of origin, factors with known phenotypic effects (see Kelly *et al.* 2010a) between 17,571 significantly expressed transcripts, and exercise and body composition-related phenotypes. In total, 36 exercise-related phenotypes and 17 traits related to food consumption, body weight and composition, and change in body weight and composition as a result of 6 days of voluntary exercise on wheels were observed. Therefore, each of the phenotypes depicted above is composed of multiple traits (*n* depicted following each phenotype) that are each highly correlated with one another (see correlation analyses in Kelly *et al.* 2010b, 2011).

or distant (following Doss *et al.* 2005). In addition, the percentage variation explained and the additive and dominance effects of each significant *cis*- and *trans*-acting eQTL were estimated in R/qtl (see Kelly *et al.* 2011).

Exclusion mapping analysis

For a subset of candidate genes uncovered by eQTL analysis, we examined gene regions to determine if the haplotypes of the parental strains (HR and B6) were identical by descent (IBD) utilizing SNPs from the Mouse Diversity array (Yang *et al.* 2009). We genotyped a subset of representative individuals from the F_0 parental strains (n =12, HR; n =1, B6) using the complete Mouse Diversity array containing 623,124 SNPs. We utilized these SNPs to determine (1) whether the interval is homozygous or heterozygous in each sample and (2) whether samples are IBD in each homozygous interval. As previously described in Farber *et al.* (2011), we determined the frequency of heterozygous calls in windows of 200 consecutive SNPs in each one of the 12 HR individuals independently. We then identified intervals that are IBD among all 12 HR founders and B6 using the same 200-SNP window and threshold (>97% genotype identity) approach used to identify the segregating regions (following Farber *et al.* 2011).

Results

Correlation analysis

Following Loess-Quantile normalization, 17,571 (of 45,281) transcripts were identified with a detection score (calculated across all 244 mice) ≥0.95. Non-normalized and normalized transcript files are provided in File S3, File S4, and File S5. Pearson partial correlations were generated between these transcripts and a total of 36 exercise-related phenotypes and 17 traits related to body weight, body composition, and change in body weight and composition as a result of 6 days of exercise. Correlations were adjusted for factors with known phenotypic effects (sex and parent of origin). After adjustment for multiple testing, 348 (∼0.04% of total possible) partial correlations were found to be statistically significant ($P \leq 0.05$), indicating putative functional relevance (Figure 1). Relationships between exercise-related traits and transcript levels accounted for the largest proportion (61.8%) of observed significant correlations (Figure 1). Among the exercise traits, running duration represented the largest percentage of significant relationships with transcript levels (48.6%). Collectively, body weight and composition-related traits accounted for 37.3% of significant correlations (Figure 1). Changes in body weight and composition, as a result of 6 days of exercise, represented only 0.006% of significant correlations with transcript levels. Greatest-magnitude correlations between exercise/body composition traits and transcript levels are presented in Table S1.

Notably, adjusted partial correlations revealed that *Insig2* was significantly correlated with body mass *post* exercise ($r = -0.33$, $P = 0.0166$; top correlation, see Table S1), with running duration on day 1 ($r = 0.30$, $P = 0.0362$), with the trajectory of running duration across all 6 days ($r = -0.34$, $P = 0.0084$), and with the intercept of running duration ($r = 0.32$, $P = 0.0084$).

eQTL analysis

In total, 2441 *cis*-acting and 2164 *trans*-acting statistically significant eQTL were observed (Figure 2, A and B). *Cis*-acting eQTL were distributed genome-wide. The average LOD score for *cis*-acting eQTL was 18.7 (range = 4.3–108.2), while for *trans*-acting eQTL the mean LOD score was 15.0 with a range of 4.3–92.9. Among 100 randomly selected, statistically significant, *trans*-acting eQTL the average size of the 95% C.I. (defined by one LOD drop) was 15.9 Mb

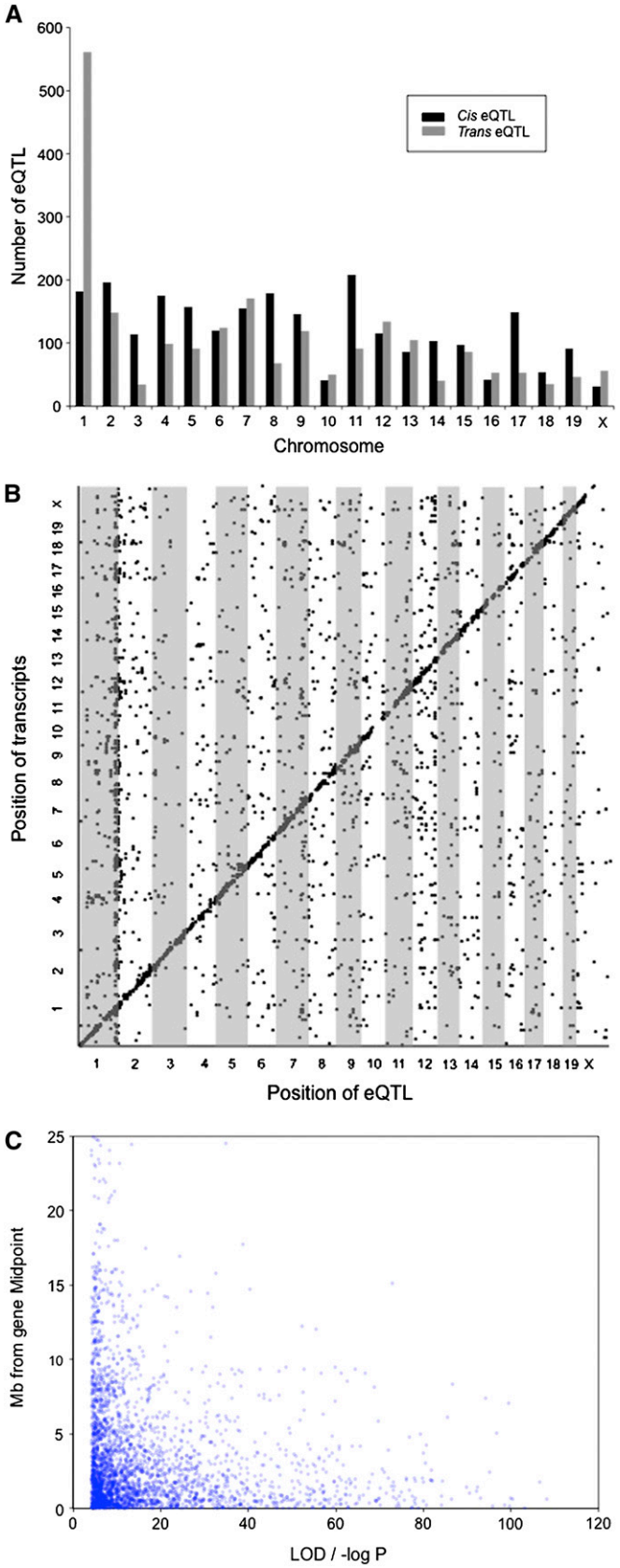

Figure 2 (A) The number of local or *cis*-acting (black bars) and distant or *trans*-acting (gray bars) eQTL across all chromosomes with a LOD ≥ 4.3. (B) Physical gene location as a function of mapped position of each QTL. The prominent diagonal band indicates *cis*-acting eQTL. A potential master regulatory region is observed on the distal end of chromosome 1, as indicated by a prominent vertical *trans*-band. Complete data file utilized to generate Figure 2B is provided in File S6. (C) *Cis*-acting eQTL were defined as falling within 10 Mb of the gene's physical location, with the most significant eQTL generally being the closest to the gene's midpoint.

(median = 15.3 Mb) with an average of 30.5 (median = 24.0) transcripts physically residing with the C.I.'s. Among *cis*-acting eQTL, the median distance of the mapped location to the midpoint of the physical location of the gene was 1.94 Mb, and the distance was negatively correlated with the significance level (Figure 2C). For comparison, in early generations of a mouse recombinant inbred strain panel, the pre-Collaborative Cross, the median liver eQTL-gene distance was 0.92 Mb (Aylor *et al.* 2011). In addition, in an outbred mouse population (MF1 stock; Harlan, Indianapolis), the median distance of eQTL peak markers from the physical gene location was 0.67 Mb, and for 25% of the genes eQTL-gene distance was <300 kb (Ghazalpour *et al.* 2008). *Trans*-acting eQTL were identified on all chromosomes, with a potential master regulatory region observed on the distal end of Chr. 1 at ~170–180 Mb based; 332 *trans*-acting eQTL mapping to this region (Figure 2B).

Significant *cis*-acting eQTL individually explained, on average, 26.35% of the total phenotypic variation for mRNA abundance of the underlying transcript, with a median percentage variance explained of 19.63% and a range of 0.45–86.65%. Average additive effects for *cis*-acting eQTL were almost universally statistically significant (98.4% or 2404 of 2441), with increasing expression as a result of the HR allele comprising ~42% (n = 998) and increasing expression as a result of the B6 allele comprising ~58% (n = 1406) of the total. In addition, average dominance effects were generally small with little statistical significance. Furthermore, we observed significant dominance effects only in the absence of significant additive effects for three *cis*-acting eQTL: *BC020354* (Chr. 20, gene location: ~147.42 Mb; eQTL location: 138.78 Mb); *Slc22a17* (Chr. 14, gene location: ~55.53 Mb; eQTL location: 63.19 Mb); and *Arrdc4* (Chr. 7, gene location: ~75.89 Mb; eQTL location: 76.26 Mb). Uniquely, *Arrdc4* mapped under a previously detected QTL (82.6 Mb, C.I. = 75–86 Mb) for running duration on day 1 (of a 6-day exposure to running wheels), which also displayed significant dominance effects in the absence of significant additive effects (Kelly *et al.* 2010b).

Significant *trans*-acting eQTL individually explained, on average, 10.38% of the total phenotypic variation for mRNA abundance of the underlying transcript with a median percentage variance explained of 8.74% and a range of 0.01–86.90%. Average additive effects for *trans*-acting eQTL were generally large and frequently statistically significant (76.7% or 1659 of 2164), with increasing effects as a result of the HR allele comprising ~49.5% (n = 821) and increasing effects as a result of the B6 alleles comprising ~50.5%

(n = 838) of the total. In addition, average dominance effects were large and statistically significant for 673 eQTL. Among these *trans*-acting eQTL, dominance was frequently found in the absence of significant additive effects. *Trans*-eQTL composing the potential master regulatory region located on the distal end of Chr. 1 similarly displayed additive effects that were frequently significant. Significant dominance effects were also noted for 102 of 332 eQTL located in the potential master regulatory region.

Using the larger G_4 population of which a subset was analyzed in the present study, we previously identified 39 significant and 18 suggestive QTL representing various exercise traits (Kelly *et al.* 2010b). Here, we compared the locations of *cis*-acting eQTL within the C.I.'s (defined by 1 LOD drop) of QTL observed for subsets of the mean exercise traits (distance, duration, average speed, and maximum speed) on days 1 and 2 (Figure 3B) and on days 5 and 6 of the 6-day wheel-access period (Figure 3, A and C–F).

Comparisons between *cis*-acting eQTL and running distance QTL (mean on days 5 and 6) revealed 30 positional candidate genes on Chr. 7 (Figure 3A and Table S2), all with significant additive effects and little dominance. For running distance on day 1, 20 potential candidate genes were identified under 2 QTL on Chr. 1, with all having significant additive effects with little dominance. On day 2, 17 overlapping candidate genes were identified under one significant QTL (Figure 3B and Table S2). For mean running duration on days 5 and 6, we identified 40 candidate genes on Chr. 7, with 30 overlapping with running distance (Figure 3C and Table S2). The additional 10 candidate genes unique to running duration resulted from an expansion of the C.I.'s for running duration loci (91–129 Mb) as compared to the C.I. for the running distance QTL (99–124 Mb) and also displayed significant additive effects. In total, we observed 50 statistically significant *cis*-acting eQTL that mapped under the previously identified QTL for an average running speed on days 5 and 6 of the 6-day wheel exposure. Thirty candidate genes were located on Chr. 2 (Figure 3D and Table S2) and the remaining 20 candidate genes were observed on Chr. 14 (Figure 3E and Table S2). Of these, similar to those described above, eQTL generally had large and statistically significant additive effects with little dominance. For maximum running speed (on days 5 and 6), 33 candidate genes were identified on Chr. 2 with 30 overlapping with those identified for running speed (Figure 3D and Table S2). In addition, 53 candidate genes, with significant additive effects, were identified on Chr. 11 for maximum running speed (Figure 3F and Table S2).

In addition to comparisons between *cis*-acting eQTL and exercise QTL, we examined colocalizing *cis*-acting eQTL and loci previously identified for change in body weight and body composition in response to exercise. Comparisons between *cis*-acting eQTL and loci observed for percentage change in body mass, as a result of 6 days of exercise, revealed 18 candidate genes on Chr. 11 (Figure 4A and Table S2). For percentage change in percentage fat mass (as described in Kelly *et al.* 2011) we identified 36 candidate genes on Chr. 1 and 40 on Chr. 5 (Figure 4, B and C; Table S2). In addition, we observed 27 candidate genes on Chr. 5 for percentage change in percentage lean mass, all of which overlapped with those identified for percentage change in percentage fat mass (Figure 4D and Table S2). In general, eQTL had large significant additive effects with little dominance.

Of the *cis*-acting eQTL identified above, *Insig2* was among the most statistically significant (LOD = 100.0; physical location: ~124 Mb) and mapped near the peaks of the following previously identified trait QTL: body mass *pre*-exercise (peak: 116 Mb), body mass *post* exercise (~106 Mb), running distance on day 1 (~113 Mb) and day 2 (~134 Mb), intercept of running distance (~123 Mb), running duration on day 1 (~136 Mb), trajectory of running duration (~123 Mb), and intercept of running duration (~134 Mb). *Insig2* was also mapped to ~83.0 Mb on Chr. 7 (*trans*-acting, LOD = 7.4). In addition, *IL15* (physical location: Chr. 8 at ~84.86 Mb) was mapped (83.9 Mb, LOD = 45.9) under previously identified loci for percentage fat mass and percentage lean mass (post exercise; see Kelly *et al.* 2011). Two additional *cis*-acting candidate genes of interest (discussed below) were *prolylcarboxypeptidase*, *angiotensinase C* (*Prcp*: physical location: Chr. 7 at ~100.08 Mb), which mapped to 93.0 Mb (LOD = 99.5); and *Arrdc4* (physical location = Chr. 7 at ~75.89 Mb), which mapped to 76.3 Mb (LOD = 4.4). Both potential candidate genes mapped under previously identified loci for exercise related traits.

Exclusion mapping

In isolated cases, we characterized the pattern of haplotype diversity in the founders. The haplotype analysis was used to identify if the select candidate genes fell within a region of IBD, making them a lower priority, or in segregating regions, making them a higher priority. We performed a detailed investigation of the *cis*-acting eQTL for *Insig2*, *IL15*, *Prcp*, and *Arrdc4*. These loci were chosen because they were among the most statistically significant and/or because they directly mapped under the confidence intervals of a variety of previously identified phenotypic QTL related to exercise and/or body composition. On the basis of the characterization of the pattern of haplotype diversity in the founders, we concluded that *Insig2*, *IL15*, *Prcp*, and *Arrdc4* all fell within a segregating region of the genome as opposed to IBD regions.

Discussion

Only two genes have been identified, on the basis of rodent studies, as potentially strong candidates involved in the regulation of physical activity: dopamine receptor 1 (*Drd1*) and nescient helix loop helix 2 (*Nhlh2*) (Lightfoot 2011). Combining QTL mapping with large-scale gene expression analysis (Jansen and Nap 2001), or eQTL mapping, is becoming increasingly commonplace in a variety of organisms (*e.g.*, Druka *et al.* 2010; Liu 2011; Parts *et al.* 2011) and has

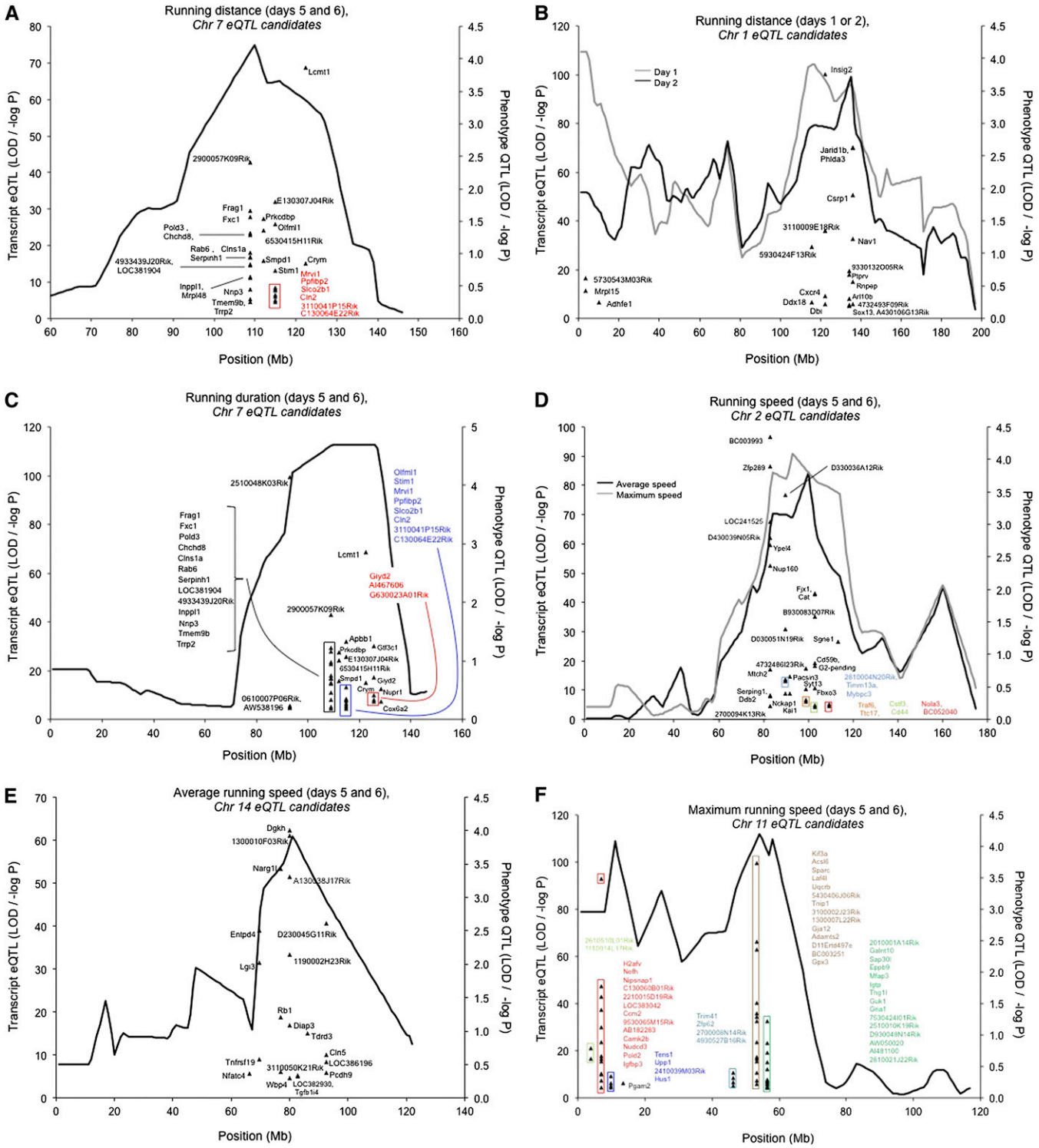

Figure 3 *Cis*-acting eQTL colocalizing with exercise QTL. Colocalizing candidate genes that fell within the confidence intervals of the trait QTL are depicted. The LOD score of the eQTL is shown on the left *y*-axis, the phenotype (exercise trait) LOD score on the right *y*-axis, and the position of both on the *x*-axis. Each transcript is labeled, and color is used only for the purpose of demarcation. Inset lists of transcripts are in the corresponding order of their vertical position. (A) Mean running distance (Chr. 7) on days 5 and 6 of a 6-day test. (B) Running distance (Chr. 1) on each of days 1(black line) and 2 (gray line). (C) Mean running duration (Chr. 7) on days 5 and 6 of a 6-day test. (D) Average (black line) and maximum (gray line) running speed (Chr. 2) on days 5 and 6 of a 6-day test. (E) Average running speed (Chr. 14) on days 5 and 6 of a 6-day test. (F) Maximum running speed (Chr. 11) on days 5 and 6 of a 6-day test.

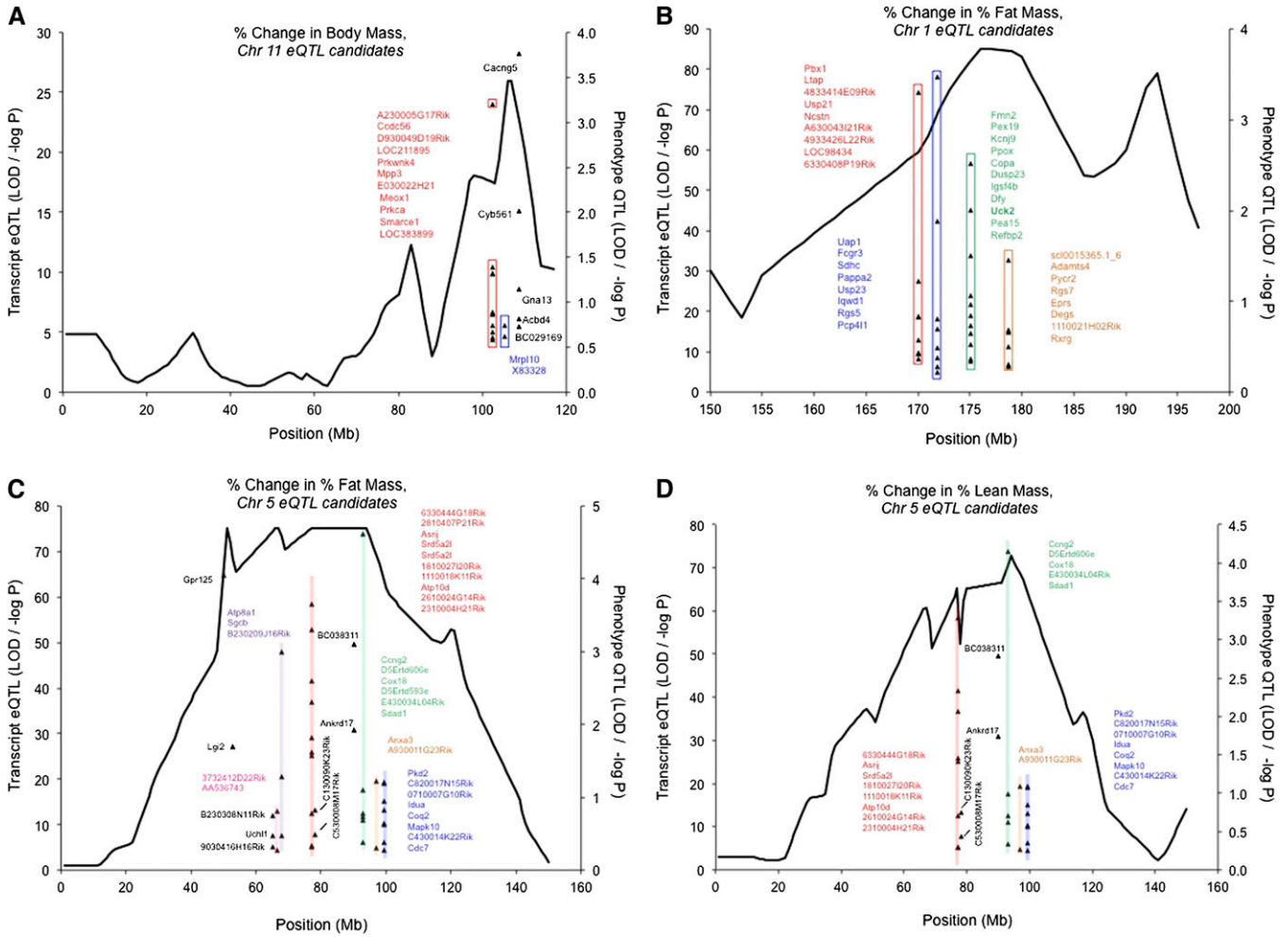

Figure 4 *Cis*-acting eQTL, colocalizing with QTL underlying changes in body weight and composition in response to 6 days of voluntary wheel running (Kelly *et al.* 2010b). Colocalizing candidate genes that fell within the confidence intervals of the trait QTL are depicted. The LOD score of the eQTL is shown on the left *y*-axis, the phenotype (exercise trait) LOD score on the right *y*-axis, and the position of both on the *x*-axis. Each transcript is labeled, and color is used only for the purpose of demarcation. Inset lists of transcripts are in the corresponding order of their vertical position. (A) Percentage change in body mass (Chr. 11). (B) Percentage change in percentage fat mass (Chr. 1). (C) Percentage change in percentage fat mass (Chr. 5). (D) Percentage change in percentage lean mass (Chr. 5).

made the selection of candidate genes underlying predisposition loci more efficient. Here we used approaches similar to those described by Lightfoot (2011) to identify candidate genes potentially playing a role in the regulation of voluntary exercise (wheel running), body composition, and their interactions. For specific candidate genes, we discuss these analyses in the context of existing functional studies. To our knowledge, an approach that bridges the gap between the neurophysiology of, and genetic predisposition to, voluntary exercise and body composition-related traits has not been addressed.

Mode of gene action

Here, we examined the percentage of phenotypic variance explained and the average additive and dominance effects of all statistically significant *cis*- and *trans*-acting eQTL (n = 4605 in total). While the *cis*-acting eQTL, on average, explained a much higher percentage (more than twice the amount) of the total phenotypic variation, the range of variance explained by *cis*- and *trans*-acting eQTL was very similar (0.45–86.65% *vs.* 0.01–86.90%, respectively). Some *trans*-acting eQTL explained a very high percentage of the total phenotypic variation, and this can in part be explained by how we chose to define *trans*-acting eQTL: as the eQTL located >10 Mb from the gene's physical midpoint. Therefore, per this definition, derived from statistical effects not biological ones (see Schadt *et al.* 2003), a *trans*-acting eQTL may be mapped to the same chromosome and even as close as 10.5 Mb from the physical midpoint of the gene. However, this was certainly not the rule, as the *trans*-acting eQTL that explained the highest percentage of phenotypic variance (86.90%) were not mapped to the same chromosome as the physical location of the gene. Although average additive effects were generally large across all eQTL, they were large and most pervasive for *cis*-acting eQTL (98.4% as opposed to 76.7% for *trans*-acting of the total). Conversely to what was observed for additive effects, dominance appeared to play a lesser

role for the *cis*-acting eQTL, while, for the *trans*-acting eQTL, dominance effects were more frequently large and statistically significant.

Similar differences, as noted here, in mode of gene action have been previously observed in an F_1 hybrid diversity panel of *Arabidopsis thaliana* (Zhang *et al.* 2011). Zhang *et al.* tested 21,803 expression traits (from the fifth or sixth true leaf) with 56,819 genome-wide SNPs and observed a tendency for locally associated SNPs to be additively inherited, while distantly related SNPs were mostly dominant. Zhang *et al.* (2011) also observed that additive effects were generally larger than dominant ones and more frequently fell into local regulatory regions.

Although the increasing effects resulting from each of the founder alleles (HR and B6) were nearly identical among the *trans*-acting eQTL, among the *cis*-acting eQTL increasing effects as a result of the B6 allele were more pervasive. The allelic bias among *cis*-acting eQTL may potentially reflect probe bias toward the strain-specific reference genome used to design microarray probes or directional detection of functional polymorphisms (see Verdugo *et al.* 2010). Alternatively, the differences in gene action between HR and B6 may be reflective of different historical selective forces, a chief difference being the artificial selection of the HR strain for increased voluntary activity.

Identification of potential candidate genes

Many genes were identified with multiple lines of evidence implicating them as candidates for exercise QTL; here we discuss selected examples only. While we discuss single candidate genes here, we acknowledge that the combined effects of multiple linked eQTL could potentially cause phenotypic QTL. One highly significant (LOD = 100.0) *cis*-acting eQTL located on Chr. 1 (~123.2 Mb), *Insig2* (insulin-induced gene 2), colocalized with loci previously identified for exercise and body composition-related traits. *Insig2* has been implicated in the functional regulation of lipid and cholesterol metabolism, positively (Herbert *et al.* 2006; Lyon *et al.* 2007) and negatively (Dina *et al.* 2007) associated with human obesity, associated with cholesterol biosynthesis, and characterized as a strong candidate susceptibility gene for total plasma cholesterol levels.

A subnetwork of *Insig2* consisted of several additional genes (*BC014805*, *Socs2*, and *Mod1*) also implicated in obesity phenotypes (Cervino *et al.* 2005). In the present study, a *trans*-acting eQTL was mapped for *Socs2* (physically located on Chr. 10 at ~94.8 Mb) to Chr.1 at 170 Mb, a locus previously identified for percentage change in percentage adiposity in response to 6 days of wheel running.

Interleukin (IL)-15α (cytokine-specific receptor) knockout mice have been shown to exhibit a leaner phenotype with lower fat composition, elevated home-cage activity and heat dissipation (light and dark phases), greater food intake (light phase only), and raised oxygen consumption (light phase only) (He *et al.* 2010). In the present study, an eQTL for *IL15* was mapped to Chr. 8 (*cis*-acting, LOD = 45.9) and Chr. 1 (*trans*-acting, LOD = 5.5), colocalizing with previously identified QTL for body composition and wheel-running traits, respectively. Furthermore, *IL15* expression level was significantly correlated with running duration, body mass, and percentage fat mass.

Prcp was found to be a highly significant (LOD = 99.5) *cis*-acting eQTL mapped to 93.0 Mb on Chr. 7, a region contained within the confidence intervals of previously (see Kelly *et al.* 2010b) identified QTL for running distance and duration (see Figure 3C and Kelly *et al.* 2010b). Wallingford *et al.* (2009) observed that the inhibition of *Prcp* activity *in vivo* decreased food intake in wild-type and obese mice, and *Prcp*-null mice were leaner and shorter than wild-type controls and resistant to high-fat diet-induced obesity (Wallingford *et al.* 2009). Similar phenotypes have been observed in the HR strain of mice utilized here (Swallow *et al.* 1999; Kelly *et al.* 2006; Vaanholt *et al.* 2008).

A *cis*-acting eQTL for *Arrdc4* was mapped under a previously detected QTL for running duration on day 1, and notably both the QTL and eQTL displayed significant dominance effects in the absence of significant additive effects. *Arrdc4* has been shown to alter glucose metabolism (Patwari *et al.* 2009), and in cancer cells is induced under lactic acidosis and repressed with glucose deprivation (Chen *et al.* 2010). Notably, HR mice have previously demonstrated adaptive plasticity in GLUT-4 abundance (Gomes *et al.* 2009), possibly indicating that the relationship between running duration and glucose usage may be facilitated through *Arrdc4*.

A final candidate, *DBY* or Ddx3y [DEAD (Asp-Glu-Ala-Asp) box polypeptide 3], is located on the Y-chromosome gene. We did not attempt to map eQTL for *DBY* (due to a lack of markers on the Y chromosome), but did identify several highly significant correlations between *DBY* expression levels and exercise and body composition traits (see Table S1). The significant correlations were large and were present only when relationships were not adjusted for sex or parent-of-origin type. *Dby* mRNA is retained in mouse spermatozoa and important for male zygotic development, possibly implicating a mechanistic role for spermatozoa mRNA during embryonic stages (Yao *et al.* 2010a,b). Previously, we demonstrated significant parent-of-origin effects on a variety of exercise and body composition traits, with these effects being most pronounced for males in some cases (Kelly *et al.* 2010a). Given the current results, we hypothesize that *DBY*, via the early environment of the zygote, may in part explain the large parent-of-origin effects.

Limitations to the current approach

Perhaps surprisingly, genes regulating dopamine signaling were not expressed above background in the present study. While other studies (*e.g.*, Bronikowski *et al.* 2004; Mathes *et al.* 2010) have targeted specific brain regions (*e.g.*, dorsal striatum and nucleus accumbens, hippocampus), we chose to use the entire right hemisphere of the brain, which may have caused significant signal dilution and, in effect, led us to miss additional important candidate genes. We acknowledge that an alternative approach would have been to target a specific brain

region previously implicated in the regulation of exercise behavior (see Introduction for examples). In our opinion, there is no one particular brain region sufficient to account for the diversity of behavioral and physiological traits measured in the G_4 population (*e.g.*, running distance, weight regulation, food consumption). Our compromise was to bisect the hemispheres, run our initial expression assays on one hemisphere, and reserve the remaining hemisphere for potential follow-up studies in a more focused/targeted fashion. This strategy, we believe, takes advantage of the fact that 186 of the top 500 genes expressed in the brain are expressed in all cell types (Lein *et al.* 2006).

In addition to not utilizing a localized brain region, we also recognize the possible limitations of the current QTL/microarray approach of identifying candidate genes (potential limitations are discussed at length in Verdugo *et al.* 2010). While we acknowledge these potential pitfalls, they did not restrict our approach to the current eQTL analysis. Therefore, although we provide supporting evidence for the proposed potential candidate genes above, we acknowledge that our results are most strongly relevant to the current methods, and caution should be taken when generally extrapolating these findings. In addition to the support provided here, additional lines of evidence will be needed (described in Lightfoot 2011) to validate the functional role of these candidate genes, especially with regard to voluntary exercise behavior. Regardless, the proximate goal of the integrative genomics approach adopted here is efficient gene discovery relevant to predisposition to engage in voluntary activity and the resultant modification of body composition. The ultimate goal is to use these results to adopt better-informed approaches to using physical activity as a preventative and therapeutic treatment for chronic disease.

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Functional Genomic Architecture of Predisposition to Voluntary Exercise in Mice: Expression QTL in the Brain

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Files S1-S5

Supporting Data

Files S1-S5 are available for download at http://www.genetics.org/content/suppl/2012/03/30/ genetics.112.140509.DC1.

File S1 - Complete genotypes.

File S2 - Following Gordon *et al.* (2010), transcript expression profiles were normalized using Loess-Quantile normalization methods with R v 2.8.1 statistical software (R Development Core Team; www.r-project.com, lumi package).

Files S3-S5 - Non-normalized and normalized transcript files.

Table S1 Top correlations (partial, adjusted for sex and parent of origin) between exercise / body composition traits and transcript levels

ProbeID	Gene Symbol	Exercise / Body Composition Trait	*n*	Partial *r*
		Running distance		
ILMN_2961216	Slco2a1	*Day* 1	234	0.3138*
ILMN_2729958	Hist1h3d			
ILMN_2768972	Fam107a	*Day* 2	234	0.3090*
ILMN_2899599	DBY			
ILMN_1227564	A930003O13	*Day* 3	240	0.3509*
ILMN_2899599	DBY			
ILMN_2763294	Ensa	*Day* 4	217	-0.3374*
ILMN_2951691	Hist1h3h			
ILMN_2768972	Fam107a	*Day* 5	244	0.3223*
ILMN_2729958	Hist1h3d			
ILMN_1247361	Abhd12	*Day* 6	244	0.3634*
ILMN_2729958	Hist1h3d			
ILMN_2768972	Fam107a	(*Days* 5 + 6)/2	244	0.3554*
ILMN_2729958	Hist1h3d			
ILMN_1222194	Tln2	Slope (*days* 1-6)	207	-0.2900
ILMN_1222194	Tln2			
ILMN_2990229	Snrnp25	Intercept (*days* 1-6)	207	-0.2889
ILMN_2899599	DBY			
		Running time		
ILMN_1225769	Clasp1	*Day* 1	234	-0.3331*
ILMN_2899599	DBY			
ILMN_2768972	Fam107a	*Day* 2	234	0.3274*
ILMN_2899599	DBY			
ILMN_2742840	Gpr34	*Day* 3	240	-0.3847*
ILMN_2899599	DBY			
ILMN_2951691	Hist1h3h	*Day* 4	217	0.4074*
ILMN_2951691	Hist1h3h			
ILMN_2951691	Hist1h3h	*Day* 5	244	0.3771*
ILMN_2951691	Hist1h3h			
ILMN_2951691	Hist1h3h	*Day* 6	244	0.3330*
ILMN_2951691	Hist1h3h			
ILMN_2951691	Hist1h3h	(*Days* 5 + 6)/2	244	0.4381*
ILMN_1234453	Hist1h3h			
ILMN_2628567	Phlda3	Slope (*days* 1-6)	207	-0.3853*
ILMN_2628567	Phlda3			
ILMN_2628567	Phlda3	Intercept (*days* 1-6)	207	0.3558*
ILMN_2899599	DBY			

		Average running speed		
ILMN_2961216	Slco2a1	*Day* 1	234	0.3116*
ILMN_2509327	Wipf3			
ILMN_2847787	Emr1	*Day* 2	234	-0.3189*
ILMN_2768972	Fam107a			
ILMN_2619107	Lgals1	*Day* 3	240	-0.3125*
ILMN_1228867	TCR-alpha			
ILMN_2619107	Lgals1	*Day* 4	217	-0.3062*
ILMN_2619107	Lgals1			
ILMN_1222543	Ugt1a6a	*Day* 5	244	0.3132*
ILMN_1222543	Ugt1a6a			
ILMN_1222543	Ugt1a6a	*Day* 6	244	0.3235*
ILMN_1222543	Ugt1a6a			
ILMN_1222543	Ugt1a6a	(*Days* 5 + 6)/2	244	0.3252*
ILMN_1222543	Ugt1a6a			
ILMN_2685150	Tmub2	Slope (*days* 1-6)	207	-0.2905
ILMN_2685150	Tmub2			
ILMN_2847787	Emr1	Intercept (*days* 1-6)	207	-0.3069
ILMN_2847787	Emr1			
		Maximum running speed		
ILMN_1240553	Htra2	*Day* 1	234	0.2635
ILMN_1257365	Thra			
ILMN_3135781	Anxa3	*Day* 2	234	-0.2792
ILMN_1250057	D10Ertd610			
ILMN_1250057	D10Ertd610	*Day* 3	240	0.2726
ILMN_1250057	D10Ertd610			
ILMN_1250057	D10Ertd610	*Day* 4	217	0.2618
ILMN_2765513	Kif3a			
ILMN_1252338	Cyp2d22	*Day* 5	244	0.2730
ILMN_2675289	Amn			
ILMN_1252338	Cyp2d22	*Day* 6	244	0.2589
ILMN_2719794	BC003331			
ILMN_1252338	Cyp2d22	(*Days* 5 + 6)/2	244	0.2717
ILMN_2675289	Amn			
ILMN_2685150	Tmub2	Slope (*days* 1-6)	207	-0.2607
ILMN_2482178	Ociad2			
ILMN_2624854	Gstm2	Intercept (*days* 1-6)	207	-0.2990*
ILMN_1224331	A830006F12			
ILMN_2678336	Ctf1	Food intake	243	-0.2796
ILMN_1244316	Hbb-b1			
ILMN_1229203	Hbb-b1	Food intake / g	242	0.3043*
ILMN_2899599	DBY			

		~8 wk of age		
ILMN_1233149	AK038694	Body mass, g	243	0.3546*
ILMN_2899599	DBY			
ILMN_2984110	Plvap	% Fat	243	0.3198*
ILMN_1244316	Hbb-b1			
ILMN_2692723	Lpl	% Lean	243	-0.2823
ILMN_2981689	Nup133			
		Post exercise		
ILMN_2690256	Insig2	Body mass, g	243	-0.3348*
ILMN_2899599	DBY			
ILMN_2825109	Zfp330	% Fat	243	-0.3422*
ILMN_2825109	Zfp330			
ILMN_2825109	Zfp330	% Lean	243	0.3431*
ILMN_2638354	Prdx2			
ILMN_1229203	Hbb-b1	% Change in body mass	243	0.2522
ILMN_2937548	Hist1h4m			
ILMN_2880536	Uck2	% Change in % fat	243	-0.3149*
ILMN_2745370	Sult1a1			
ILMN_2622089	5430432N15	% Change in % lean	243	0.2695
ILMN_2622089	5430432N15			

*P < 0.05, **P < 0.001

Table S2 Candidate genes based on proximity to QTL for exercise and change in body weight/composition in response to exercise. For partial (adjusted for sex and parent of origin) correlations, * indicates significance at P ≤ 0.05 after correction for multiple comparisons

ProbeID	Gene Symbol	Chr	LOD	eQTL peak (Mb)	eQTL to Gene (Mb)	eQTL to QTL (Mb)	Partial *r*
			Running Distance, (Days 5+6)/2				
ILMN_1215550	Inppl1	7	11.1	108.92	0.05	0.02	0.09
ILMN_1220948	Trrp2	7	4.5	108.92	0.31	0.02	-0.11
ILMN_1215818	4933439J20Rik	7	14.7	108.92	0.31	0.02	-0.04
ILMN_1235347	Frag1	7	29.5	108.92	0.47	0.02	0.02
ILMN_2540464	LOC381904	7	14.9	108.92	1.09	0.02	0.03
ILMN_1242802	Rab6	7	16.9	108.92	1.14	0.02	-0.04
ILMN_1236131	Mrpl48	7	11.5	108.92	1.22	0.02	-0.10
ILMN_2817151	Chchd8	7	22.9	108.92	1.23	0.02	0.18
ILMN_2720995	Pold3	7	23.5	108.92	1.69	0.02	-0.02
ILMN_2760568	2900057K09Rik	7	42.9	108.92	1.85	0.02	0.00
ILMN_2777359	Serpinh1	7	16.8	108.92	2.42	0.02	-0.01
ILMN_2824723	Fxc1	7	27.7	108.92	3.87	0.02	0.03
ILMN_2649083	Clns1a	7	18.2	108.92	4.07	0.02	0.09
ILMN_2914884	Tmem9b	7	5.3	108.92	7.96	0.02	0.06
ILMN_2875404	Nrip3	7	8.0	108.92	7.98	0.02	0.05
ILMN_1232971	6530415H11Rik	7	24.2	112.05	0.47	3.15	0.01
ILMN_2956942	Prkcdbp	7	27.5	112.05	0.58	3.15	-0.06
ILMN_2868987	Smpd1	7	15.9	112.05	0.65	3.15	0.01
ILMN_2964841	Ppfibp2	7	7.8	114.94	0.05	6.04	0.08
ILMN_1219253	Olfml1	7	13.2	114.94	0.20	6.04	-0.12
ILMN_1216534	E130307J04Rik	7	25.8	114.94	1.25	6.04	-0.04
ILMN_1216341	3110041P15Rik	7	5.1	114.94	2.04	6.04	-0.09
ILMN_2705991	Cln2	7	6.0	114.94	2.04	6.04	-0.02
ILMN_2623591	Apbb1	7	32.0	114.94	2.23	6.04	-0.03

ILMN_1221892	C130064E22Rik	7	4.6	114.94	2.24	6.04	-0.06
ILMN_2746283	Mrvi1	7	8.0	114.94	3.07	6.04	0.09
ILMN_1216313	Stim1	7	8.6	114.94	5.52	6.04	-0.02
ILMN_2619707	Slco2b1	7	6.5	114.94	8.13	6.04	-0.14
ILMN_2913563	Crym	7	15.1	122.38	4.95	13.48	-0.03
ILMN_2758728	Lcmt1	7	68.7	122.38	8.14	13.48	0.09
Running Distance, Day 1							
ILMN_1250779	5730543M03Rik	1	16.6	3.46	1.31	0.04	-0.07
ILMN_1252743	Mrpl15	1	11.5	3.46	1.32	0.04	0.12
ILMN_2675064	Adhfe1	1	6.6	9.99	0.45	6.49	-0.03
ILMN_1225769	5930424F13Rik	1	29.4	115.56	4.84	2.86	-0.26
ILMN_1246999	Ddx18	1	6.5	115.56	7.89	2.86	0.08
ILMN_1235047	3110009E18Rik	1	35.9	122.52	0.44	9.82	-0.23
ILMN_3150159	Dbi	1	5.8	122.52	0.51	9.82	0.11
ILMN_2690256	Insig2	1	100.0	122.52	0.68	9.82	0.23
ILMN_2630459	Cxcr4	1	9.4	122.52	7.96	9.82	-0.04
ILMN_1244292	Sox13	1	5.3	134.31	0.97	21.61	0.03
ILMN_2625197	Ptprv	1	18.2	134.31	2.70	21.61	0.01
ILMN_2680781	Arl10b	1	8.0	134.31	2.74	21.61	0.11
ILMN_2775402	9330132O05Rik	1	19.4	134.31	2.96	21.61	-0.17
ILMN_1228804	A430106G13Rik	1	5.4	134.31	5.56	21.61	-0.13
ILMN_2777722	Jarid1b	1	70.2	136.28	0.25	23.58	0.19
ILMN_1246024	Rnpep	1	14.9	136.28	0.88	23.58	0.16
ILMN_2883016	Nav1	1	32.8	136.28	1.06	23.58	0.13
ILMN_1260378	Csrp1	1	50.5	136.28	1.37	23.58	0.13
ILMN_2628567	Phlda3	1	70.1	136.28	1.39	23.58	0.22
ILMN_2639579	4732493F09Rik	1	6.0	136.28	6.44	23.58	-0.02
Running Distance, Day 2							
ILMN_1225769	5930424F13Rik	1	29.4	115.56	115.56	18.74	-0.22
ILMN_124699	Ddx18	1	6.5	115.56	115.56	18.74	0.12

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ILMN_1235047	3110009E18Rik	1	35.9	122.52	122.52	11.78	-0.17
ILMN_3150159	Dbi	1	5.8	122.52	122.52	11.78	0.17
ILMN_2690256	Insig2	1	100.0	122.52	122.52	11.78	0.23
ILMN_2630459	Cxcr4	1	9.4	122.52	122.52	11.78	-0.01
ILMN_1244292	Sox13	1	5.3	134.31	134.31	0.01	0.02
ILMN_2625197	Ptprv	1	18.2	134.31	134.31	0.01	-0.13
ILMN_2680781	Arl10b	1	8.0	134.31	134.31	0.01	0.13
ILMN_2775402	9330132O05Rik	1	19.4	134.31	134.31	0.01	-0.21
ILMN_1228804	A430106G13Rik	1	5.4	134.31	134.31	0.01	-0.21
ILMN_2777722	Jarid1b	1	70.2	136.28	136.28	1.98	0.22
ILMN_1246024	Rnpep	1	14.9	136.28	136.28	1.98	0.12
ILMN_2883016	Nav1	1	32.8	136.28	136.28	1.98	0.13
ILMN_1260378	Csrp1	1	50.5	136.28	136.28	1.98	0.19
ILMN_2628567	Phlda3	1	70.1	136.28	136.28	1.98	0.19
ILMN_2639579	4732493F09Rik	1	6.0	136.28	136.28	1.98	-0.03
			Running Duration, (Days 5+6)/2				
ILMN_3162224	0610007P06Rik	7	5.6	93.00	4.07	15.90	0.20
ILMN_1255175	AW538196	7	4.8	93.00	5.53	15.90	0.10
ILMN_2639155	2510048K03Rik	7	99.5	93.00	7.08	15.90	-0.09
ILMN_1215550	Inppl1	7	11.1	108.92	0.05	0.02	0.16
ILMN_1220948	Trrp2	7	4.5	108.92	0.31	0.02	-0.08
ILMN_1215818	4933439J20Rik	7	14.7	108.92	0.31	0.02	-0.15
ILMN_1235347	Frag1	7	29.5	108.92	0.47	0.02	-0.09
ILMN_2540464	LOC381904	7	14.9	108.92	1.09	0.02	0.11
ILMN_1242802	Rab6	7	16.9	108.92	1.14	0.02	-0.13
ILMN_1236131	Mrpl48	7	11.5	108.92	1.22	0.02	-0.14
ILMN_2817151	Chchd8	7	22.9	108.92	1.23	0.02	0.31*
ILMN_2720995	Pold3	7	23.5	108.92	1.69	0.02	-0.10
ILMN_276056	2900057K09Rik	7	42.9	108.92	1.85	0.02	-0.13

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ILMN_2777359	Serpinh1	7	16.8	108.92	2.42	0.02	0.04
ILMN_2824723	Fxc1	7	27.7	108.92	3.87	0.02	-0.04
ILMN_2649083	Clns1a	7	18.2	108.92	4.07	0.02	0.11
ILMN_2914884	Tmem9b	7	5.3	108.92	7.96	0.02	0.12
ILMN_2875404	Nrip3	7	8.0	108.92	7.98	0.02	0.09
ILMN_1232971	6530415H11Rik	7	24.2	112.05	0.47	3.15	-0.04
ILMN_2956942	Prkcdbp	7	27.5	112.05	0.58	3.15	-0.07
ILMN_2868987	Smpd1	7	15.9	112.05	0.65	3.15	-0.03
ILMN_2964841	Ppfibp2	7	7.8	114.94	0.05	6.04	0.05
ILMN_1219253	Olfml1	7	13.2	114.94	0.20	6.04	-0.09
ILMN_1216534	E130307J04Rik	7	25.8	114.94	1.25	6.04	-0.09
ILMN_1216341	3110041P15Rik	7	5.1	114.94	2.04	6.04	-0.02
ILMN_2705991	Cln2	7	6.0	114.94	2.04	6.04	-0.06
ILMN_2623591	Apbb1	7	32.0	114.94	2.23	6.04	-0.10
ILMN_1221892	C130064E22Rik	7	4.6	114.94	2.24	6.04	-0.10
ILMN_2746283	Mrvi1	7	8.0	114.94	3.07	6.04	0.20
ILMN_1216313	Stim1	7	8.6	114.94	5.52	6.04	0.00
ILMN_2619707	Slco2b1	7	6.5	114.94	8.13	6.04	-0.15
ILMN_2913563	Crym	7	15.1	122.38	4.95	13.48	-0.18
ILMN_2758728	Lcmt1	7	68.7	122.38	8.14	13.48	0.21
ILMN_1229458	Prkcb	7	7.5	125.73	4.04	16.83	-0.06
ILMN_1243678	Gtf3c1	7	30.0	125.73	7.05	16.83	-0.19
ILMN_2462901	G630023A01Rik	7	8.1	125.73	7.29	16.83	-0.16
ILMN_2732394	Giyd2	7	17.4	125.73	8.10	16.83	0.09
ILMN_1213645	AI467606	7	9.9	125.73	8.50	16.83	0.18
ILMN_2742042	Nupr1	7	12.4	128.31	5.45	19.41	-0.09
ILMN_2629581	Cox6a2	7	7.2	128.31	7.04	19.41	0.00
Average Running Speed, (Days 5+6)/2							
ILMN_121290	D430039N05Ri	2	62.1	82.78	0.95	16.22	0.12

7	k						
ILMN_3088934	2700094K13Rik	2	4.7	82.78	1.73	16.22	0.09
ILMN_2966558	Ypel4	2	59.6	82.78	1.80	16.22	0.14
ILMN_1254473	LOC241525	2	67.6	82.78	1.80	16.22	0.09
ILMN_2775421	Serping1	2	8.2	82.78	1.83	16.22	0.05
ILMN_2895293	BC003993	2	96.6	82.78	5.04	16.22	-0.07
ILMN_2756716	Nup160	2	52.5	82.78	7.80	16.22	0.04
ILMN_2848583	Mtch2	2	17.3	82.78	7.93	16.22	0.05
ILMN_2791769	Ddb2	2	7.9	82.78	8.28	16.22	-0.03
ILMN_1241481	Zfp289	2	86.6	82.78	8.34	16.22	0.12
ILMN_2602406	2810004N20Rik	2	13.7	89.55	1.20	9.45	0.08
ILMN_1229140	D330036A12Rik	2	76.7	89.55	1.21	9.45	-0.09
ILMN_2689136	Mybpc3	2	13.0	89.55	1.42	9.45	-0.07
ILMN_2760593	D030051N19Rik	2	30.8	89.55	2.21	9.45	0.05
ILMN_1227235	Timm13a	2	13.0	89.55	4.88	9.45	0.06
ILMN_1220664	Nckap1	2	8.8	89.55	9.21	9.45	0.09
ILMN_2589015	Pacsin3	2	14.6	91.83	0.73	7.17	-0.05
ILMN_2747196	Kai1	2	9.0	91.83	1.43	7.17	-0.12
ILMN_2960750	Traf6	2	6.8	99.04	2.50	0.04	0.03
ILMN_2511768	Ttc17	2	6.3	99.04	4.90	0.04	0.00
ILMN_2629307	4732486I23Rik	2	17.4	99.04	5.55	0.04	0.12
ILMN_1229379	Syt13	2	10.3	99.04	6.24	0.04	-0.06
ILMN_1223697	Cd44	2	4.4	102.76	0.10	3.76	0.01
ILMN_2737416	Fjx1	2	43.1	102.76	0.47	3.76	-0.04
ILMN_2826110	Cat	2	42.9	102.76	0.54	3.76	-0.14
ILMN_3131522	Fbxo3	2	10.6	102.76	1.14	3.76	0.06
ILMN_2660766	Cd59b	2	19.2	102.76	1.16	3.76	0.07
ILMN_1234424	G2-pending	2	18.4	102.76	1.23	3.76	0.15
ILMN_3145415	Cstf3	2	4.8	102.76	1.69	3.76	0.15

ILMN_1254133	B930083D07Rik	2	35.3	102.76	1.77	3.76	0.07
ILMN_2647331	Nfatc4	14	5.8	66.14	9.69	13.76	0.13
ILMN_2589312	Entpd4	14	39.1	69.46	0.53	10.44	-0.13
ILMN_2994995	Lgi3	14	31.6	69.46	1.48	10.44	0.20
ILMN_2793522	Tnfrsf19	14	9.1	69.46	7.88	10.44	0.02
ILMN_2680128	3110050K21Rik	14	6.2	76.86	1.14	3.04	-0.10
ILMN_2733933	Narg1l	14	53.3	76.86	2.87	3.04	-0.18
ILMN_2861644	Rb1	14	18.7	76.86	3.27	3.04	0.10
ILMN_2462762	Wbp4	14	4.7	79.90	0.04	0.00	-0.14
ILMN_2513781	A130038J17Rik	14	51.4	79.90	0.20	0.00	-0.19
ILMN_2593774	1190002H23Rik	14	33.4	79.90	0.21	0.00	0.11
ILMN_1249480	1300010F03Rik	14	61.0	79.90	0.30	0.00	-0.21
ILMN_2459211	Dgkh	14	62.4	79.90	0.90	0.00	-0.20
ILMN_2606436	Diap3	14	17.0	79.90	7.16	0.00	-0.15
ILMN_2723108	Tgfb1i4	14	5.1	82.64	5.74	2.74	0.01
ILMN_1248508	LOC382930	14	5.3	82.64	10.78	2.74	0.00
ILMN_2650683	Tdrd3	14	15.2	85.99	1.95	6.09	0.11
ILMN_1231837	Pcdh9	14	5.9	92.60	0.81	12.70	0.01
ILMN_1223901	D230045G11Rik	14	40.6	92.60	1.08	12.70	-0.17
ILMN_1214337	LOC386196	14	8.5	92.60	10.62	12.70	-0.06
ILMN_2639291	Cln5	14	10.1	92.60	10.88	12.70	-0.13
Maximum Running Speed, (Days 5+6)/2							
ILMN_1212907	D430039N05Rik	2	62.1	82.78	0.95	9.02	0.12
ILMN_3088934	2700094K13Rik	2	4.7	82.78	1.73	9.02	0.07
ILMN_1254473	LOC241525	2	67.6	82.78	1.80	9.02	0.08
ILMN_2966558	Ypel4	2	59.6	82.78	1.80	9.02	0.11
ILMN_2775421	Serping1	2	8.2	82.78	1.83	9.02	0.03
ILMN_2895293	BC003993	2	96.6	82.78	5.04	9.02	-0.10
ILMN_2756716	Nup160	2	52.5	82.78	7.80	9.02	0.06

ILMN_2848583	Mtch2	2	17.3	82.78	7.93	9.02	0.06
ILMN_2791769	Ddb2	2	7.9	82.78	8.28	9.02	-0.02
ILMN_1241481	Zfp289	2	86.6	82.78	8.34	9.02	0.12
ILMN_2602406	2810004N20Rik	2	13.7	89.55	1.20	2.25	0.09
ILMN_2760593	D030051N19Rik	2	30.8	89.55	2.21	2.25	0.07
ILMN_1227235	Timm13a	2	13.0	89.55	4.88	2.25	0.05
ILMN_1220664	Nckap1	2	8.8	89.55	9.21	2.25	0.13
ILMN_1229140	D330036A12Rik	2	76.7	89.60	1.20	2.25	-0.12
ILMN_2689136	Mybpc3	2	13.0	89.60	1.40	2.25	-0.12
ILMN_2589015	Pacsin3	2	14.6	91.83	0.73	0.03	-0.09
ILMN_2747196	Kai1	2	9.0	91.83	1.43	0.03	-0.12
ILMN_2960750	Traf6	2	6.8	99.04	2.50	7.24	0.04
ILMN_2511768	Ttc17	2	6.3	99.04	4.90	7.24	0.01
ILMN_2629307	4732486I23Rik	2	17.4	99.04	5.55	7.24	0.15
ILMN_1229379	Syt13	2	10.3	99.04	6.24	7.24	-0.06
ILMN_1223697	Cd44	2	4.4	102.76	0.10	10.96	-0.01
ILMN_2737416	Fjx1	2	43.1	102.76	0.47	10.96	-0.06
ILMN_2826110	Cat	2	42.9	102.76	0.54	10.96	-0.13
ILMN_3131522	Fbxo3	2	10.6	102.76	1.14	10.96	0.08
ILMN_2660766	Cd59b	2	19.2	102.76	1.16	10.96	0.07
ILMN_1234424	G2-pending	2	18.4	102.76	1.23	10.96	0.15
ILMN_3145415	Cstf3	2	4.8	102.76	1.69	10.96	0.16
ILMN_1254133	B930083D07Rik	2	35.3	102.76	1.77	10.96	0.04
ILMN_2669023	Nola3	2	5.1	109.20	2.90	17.40	0.01
ILMN_1227874	BC052040	2	4.6	109.20	6.41	17.40	-0.05
ILMN_2592953	Sgne1	2	26.6	113.18	0.43	21.38	-0.04
ILMN_2690772	2610510L01Rik	11	21.1	3.78	0.86	6.12	-0.16
ILMN_2906414	1110014L17Rik	11	16.8	3.78	2.39	6.12	-0.07
ILMN_2727503	Igfbp3	11	4.6	7.05	0.06	2.85	-0.02

ILMN_2719834	Ccm2	11	17.7	7.05	0.56	2.85	-0.10
ILMN_2891085	AB182283	11	15.4	7.05	0.56	2.85	-0.08
ILMN_2688345	H2afv	11	93.1	7.05	0.73	2.85	-0.13
ILMN_1217147	C130060B01Rik	11	37.6	7.05	1.02	2.85	-0.11
ILMN_1236009	Camk2b	11	10.3	7.05	1.18	2.85	0.07
ILMN_2817892	Pold2	11	7.3	7.05	1.28	2.85	0.01
ILMN_2511327	2210015D19Rik	11	29.8	7.05	1.37	2.85	-0.10
ILMN_1260331	LOC383042	11	23.6	7.05	1.37	2.85	0.14
ILMN_1214117	9530065M15Rik	11	16.8	7.05	1.80	2.85	-0.06
ILMN_1237729	Nefh	11	47.3	7.05	2.22	2.85	-0.10
ILMN_2619861	Nipsnap1	11	43.0	7.05	2.26	2.85	-0.10
ILMN_2837226	Nudcd3	11	10.0	7.10	1.00	2.85	0.10
ILMN_1225370	2410039M03Rik	11	5.2	9.90	7.20	0.04	-0.02
ILMN_2959291	Upp1	11	6.4	9.94	0.90	0.04	0.07
ILMN_1229175	Hus1	11	4.5	9.94	1.05	0.04	0.04
ILMN_2491469	Tens1	11	9.1	9.94	1.49	0.04	-0.14
ILMN_2588815	Pgam2	11	6.3	13.51	7.81	3.61	-0.03
ILMN_2652291	4930527B16Rik	11	5.1	46.24	1.96	6.96	0.05
ILMN_1260252	Trim41	11	10.9	46.24	2.38	6.96	0.02
ILMN_3144673	Zfp62	11	8.6	46.24	2.79	6.96	0.13
ILMN_1251220	2700008N14Rik	11	6.5	46.24	3.74	6.96	-0.17
ILMN_2632839	1300007L22Rik	11	17.4	53.20	0.00	0.04	-0.07
ILMN_2621148	Kif3a	11	99.7	53.20	0.20	0.04	-0.23
ILMN_1236666	Acsl6	11	66.2	53.20	0.90	0.04	-0.18
ILMN_1230726	5430406J06Rik	11	34.6	53.20	1.40	0.04	-0.12
ILMN_1251170	Laf4l	11	40.6	53.24	0.00	0.04	0.13
ILMN_1252263	Uqcrb	11	35.8	53.24	0.01	0.04	-0.10
ILMN_1236906	D11Ertd497e	11	10.9	53.24	1.45	0.04	-0.11
ILMN_2715546	Gpx3	11	6.1	53.24	1.49	0.04	0.13

ILMN_2417863	Tnip1	11	32.6	53.24	1.49	0.04	0.12
ILMN_1243212	Sparc	11	63.1	53.24	1.97	0.04	-0.19
ILMN_1226259	Adamts2	11	15.5	53.24	2.62	0.04	0.07
ILMN_2734789	BC003251	11	7.5	53.24	4.92	0.04	0.03
ILMN_2635708	3100002J23Rik	11	23.5	53.24	5.37	0.04	0.14
ILMN_2597606	Gja12	11	16.5	53.24	5.75	0.04	0.11
ILMN_2648012	Gria1	11	6.8	56.50	0.64	3.30	0.08
ILMN_3095462	Mfap3	11	12.1	56.50	0.84	3.30	-0.09
ILMN_2878781	Galnt10	11	23.3	56.50	1.10	3.30	-0.23
ILMN_1251423	2010001A14Rik	11	32.6	56.50	1.10	3.30	-0.21
ILMN_3128784	Sap30l	11	19.2	56.50	1.12	3.30	0.15
ILMN_2459720	2510010K19Rik	11	5.9	56.50	1.32	3.30	-0.09
ILMN_2593554	Igtp	11	7.7	56.50	1.52	3.30	-0.12
ILMN_1259564	AI481100	11	4.6	56.50	1.53	3.30	-0.11
ILMN_2674668	2810021J22Rik	11	4.4	56.50	2.19	3.30	0.14
ILMN_2967576	Guk1	11	7.1	56.50	2.49	3.30	0.10
ILMN_2583530	7530424I01Rik	11	6.1	56.50	3.21	3.30	-0.13
ILMN_1255259	AW050020	11	4.6	56.50	3.86	3.30	-0.03
ILMN_2713969	Eppb9	11	15.3	56.50	4.82	3.30	-0.01
ILMN_2727546	D930048N14Rik	11	4.7	56.50	5.03	3.30	-0.15
ILMN_2979430	Thg1l	11	7.4	56.50	10.74	3.30	0.04
				% Change in Body Mass			
ILMN_1247327	E030022H21	11	6.5	102.35	102.35	2.65	0.03
ILMN_1242093	A230005G17Rik	11	24.0	102.35	102.35	2.65	-0.02
ILMN_2662595	Mpp3	11	6.6	102.35	102.35	2.65	0.00
ILMN_1213886	Meox1	11	5.6	102.35	102.35	2.65	0.03
ILMN_2765287	Ccdc56	11	10.5	102.35	102.35	2.65	0.04
ILMN_2518744	Prkwnk4	11	6.7	102.35	102.35	2.65	-0.01
ILMN_1256538	LOC211895	11	9.9	102.35	102.35	2.65	0.08

ILMN_2880246	Smarce1	11	4.6	102.35	102.35	2.65	0.02
ILMN_1217890	Prkca	11	5.1	102.35	102.35	2.65	-0.06
ILMN_2582563	D930049D19Rik	11	9.9	102.35	102.35	2.65	-0.03
ILMN_1233637	LOC383899	11	4.4	102.35	102.35	2.65	0.05
ILMN_2464898	X83328	11	4.7	105.37	105.37	0.37	-0.02
ILMN_2822622	Mrpl10	11	5.6	105.37	105.37	0.37	-0.04
ILMN_2754253	Gna13	11	8.6	108.68	108.68	3.68	-0.04
ILMN_2840430	BC029169	11	5.5	108.68	108.68	3.68	-0.04
ILMN_2725698	Cacng5	11	28.3	108.68	108.68	3.68	-0.17
ILMN_1232601	Cyb561	11	15.1	108.68	108.68	3.68	0.02
ILMN_2689540	Acbd4	11	6.2	108.68	108.68	3.68	-0.16

% Change in % Fat Mass

ILMN_2424703	4933426L22Rik	1	9.6	170.02	170.02	7.98	0.05
ILMN_2914416	Ncstn	1	12.8	170.02	170.02	7.98	-0.21
ILMN_2685770	Ltap	1	27.6	170.02	170.02	7.98	-0.23
ILMN_2495939	Usp21	1	18.7	170.02	170.02	7.98	-0.10
ILMN_2545149	6330408P19Rik	1	8.2	170.02	170.02	7.98	-0.13
ILMN_2446405	LOC98434	1	9.5	170.02	170.02	7.98	-0.04
ILMN_2559669	Pbx1	1	74.2	170.02	170.02	7.98	0.16
ILMN_2748880	4833414E09Rik	1	18.7	170.02	170.02	7.98	0.13
ILMN_2570436	A630043I21Rik	1	9.6	170.02	170.02	7.98	0.09
ILMN_2608666	Iqwd1	1	8.6	171.81	171.81	6.19	0.17
ILMN_1239638	Pappa2	1	15.7	171.81	171.81	6.19	0.19
ILMN_1254123	Usp23	1	11.1	171.81	171.81	6.19	-0.08
ILMN_1254622	Pcp4l1	1	5.0	171.81	171.81	6.19	-0.11
ILMN_2594149	Sdhc	1	18.1	171.81	171.81	6.19	0.04
ILMN_2687403	Fcgr3	1	42.4	171.81	171.81	6.19	0.16
ILMN_2502542	Uap1	1	78.2	171.81	171.81	6.19	-0.20
ILMN_2979824	Rgs5	1	6.4	171.81	171.81	6.19	0.09

ILMN_2880536	Uck2	1	11.7	175.07	175.07	2.93	-0.31*
ILMN_2826816	Ppox	1	24.0	175.07	175.07	2.93	-0.14
ILMN_2697266	Refbp2	1	7.7	175.07	175.07	2.93	-0.05
ILMN_1214139	Fmn2	1	56.8	175.07	175.07	2.93	-0.18
ILMN_2681906	Copa	1	21.7	175.07	175.07	2.93	-0.15
ILMN_2970834	Pex19	1	45.2	175.07	175.07	2.93	-0.14
ILMN_2624938	Pea15	1	8.2	175.07	175.07	2.93	0.01
ILMN_1242415	Kcnj9	1	33.8	175.07	175.07	2.93	0.09
ILMN_3160863	Dusp23	1	19.0	175.07	175.07	2.93	-0.13
ILMN_1254663	Igsf4b	1	16.6	175.07	175.07	2.93	0.05
ILMN_2656748	Dfy	1	14.6	175.07	175.07	2.93	-0.12
ILMN_1232561	Rxrg	1	6.4	178.74	178.74	0.74	-0.13
ILMN_3148398	Eprs	1	11.4	178.74	178.74	0.74	0.11
ILMN_1230152	Adamts4	1	15.4	178.74	178.74	0.74	0.01
ILMN_2744693	1110021H02Rik	1	6.7	178.74	178.74	0.74	-0.13
ILMN_2709470	Degs	1	6.8	178.74	178.74	0.74	0.04
ILMN_2998548	Pycr2	1	15.1	178.74	178.74	0.74	-0.13
ILMN_1237219	Rgs7	1	14.8	178.74	178.74	0.74	-0.06
ILMN_2521893	scl0015365.1_6	1	32.8	178.74	178.74	0.74	0.11
ILMN_1251856	Gpr125	5	64.8	49.99	49.99	40.01	0.02
ILMN_2635700	Lgi2	5	27.1	52.90	52.90	37.10	-0.06
ILMN_1225261	Uchl1	5	7.6	65.04	65.04	24.96	0.09
ILMN_1220514	9030416H16Rik	5	5.0	65.04	65.04	24.96	0.05
ILMN_2457854	B230308N11Rik	5	12.0	65.04	65.04	24.96	0.06
ILMN_2656645	AA536743	5	4.3	66.45	66.45	23.55	-0.06
ILMN_2628603	3732412D22Rik	5	13.1	66.45	66.45	23.55	-0.08
ILMN_1255256	Sgcb	5	20.5	67.96	67.96	22.04	-0.05
ILMN_1249139	B230209J16Rik	5	7.6	67.96	67.96	22.04	0.05
ILMN_2509817	Atp8a1	5	48.0	67.96	67.96	22.04	0.07

ILMN_1235196	Atp10d	5	12.5	77.23	77.23	12.77	-0.11
ILMN_1225234	2310004H21Rik	5	5.2	77.23	77.23	12.77	0.00
ILMN_1244545	6330444G18Rik	5	58.5	77.23	77.23	12.77	-0.14
ILMN_1225390	Asrij	5	41.6	77.23	77.23	12.77	0.03
ILMN_2482178	1810027I20Rik	5	26.0	77.23	77.23	12.77	0.11
ILMN_1248812	Srd5a2l	5	29.0	77.23	77.23	12.77	0.03
ILMN_2683222	Srd5a2l	5	36.9	77.23	77.23	12.77	0.01
ILMN_2835461	2610024G14Rik	5	5.3	77.23	77.23	12.77	-0.04
ILMN_2548010	1110018K11Rik	5	25.1	77.23	77.23	12.77	-0.08
ILMN_2747828	2810407P21Rik	5	52.8	77.23	77.23	12.77	0.11
ILMN_3163255	C130090K23Rik	5	13.3	78.14	78.14	11.86	0.12
ILMN_2670775	C530008M17Rik	5	7.8	78.14	78.14	11.86	-0.09
ILMN_2675464	Ankrd17	5	30.9	90.09	90.09	0.09	0.08
ILMN_2633039	BC038311	5	49.6	90.09	90.09	0.09	-0.15
ILMN_3002011	Cox18	5	12.5	93.05	93.05	3.05	-0.13
ILMN_2700233	Ccng2	5	73.8	93.05	93.05	3.05	0.07
ILMN_2666747	E430034L04Rik	5	11.1	93.05	93.05	3.05	-0.15
ILMN_2449120	D5Ertd606e	5	17.6	93.05	93.05	3.05	-0.13
ILMN_1250278	Sdad1	5	6.0	93.05	93.05	3.05	0.07
ILMN_2663211	D5Ertd593e	5	11.9	93.05	93.05	3.05	0.01
ILMN_2574529	A930011G23Rik	5	4.9	96.86	96.86	6.86	0.03
ILMN_3135781	Anxa3	5	19.5	96.86	96.86	6.86	-0.01
ILMN_2980466	Idua	5	13.2	99.48	99.48	9.48	-0.01
ILMN_1237581	0710007G10Rik	5	15.1	99.48	99.48	9.48	0.06
ILMN_1238374	Cdc7	5	4.5	99.48	99.48	9.48	0.02
ILMN_2866327	Pkd2	5	19.3	99.48	99.48	9.48	-0.05
ILMN_2778112	Mapk10	5	10.0	99.48	99.48	9.48	0.21
ILMN_2557762	C430014K22Rik	5	6.2	99.48	99.48	9.48	0.06
ILMN_3009260	Coq2	5	10.4	99.48	99.48	9.48	0.04

ILMN_1232659	C820017N15Rik	5	19.2	99.48	99.48	9.48	0.07
				% Change in % Lean Mass			
ILMN_1235196	Atp10d	5	12.5	77.23	77.23	15.77	0.14
ILMN_1225234	2310004H21Rik	5	5.2	77.23	77.23	15.77	-0.06
ILMN_1244545	6330444G18Rik	5	58.5	77.23	77.23	15.77	0.07
ILMN_1225390	Asrij	5	41.6	77.23	77.23	15.77	0.00
ILMN_2482178	1810027I20Rik	5	26.0	77.23	77.23	15.77	-0.06
ILMN_2683222	Srd5a2l	5	36.9	77.23	77.23	15.77	0.01
ILMN_2835461	2610024G14Rik	5	5.3	77.23	77.23	15.77	-0.03
ILMN_2548010	1110018K11Rik	5	25.1	77.23	77.23	15.77	0.08
ILMN_3163255	C130090K23Rik	5	13.3	78.14	78.14	14.86	-0.07
ILMN_2670775	C530008M17Rik	5	7.8	78.14	78.14	14.86	0.09
ILMN_2675464	Ankrd17	5	30.9	90.09	90.09	2.91	-0.08
ILMN_2633039	BC038311	5	49.6	90.09	90.09	2.91	0.13
ILMN_3002011	Cox18	5	12.5	93.05	93.05	0.05	0.10
ILMN_2700233	Ccng2	5	73.8	93.05	93.05	0.05	-0.06
ILMN_2666747	E430034L04Rik	5	11.1	93.05	93.05	0.05	0.10
ILMN_2449120	D5Ertd606e	5	17.6	93.05	93.05	0.05	0.10
ILMN_1250278	Sdad1	5	6.0	93.05	93.05	0.05	-0.08
ILMN_2574529	A930011G23Rik	5	4.9	96.86	96.86	3.86	-0.08
ILMN_3135781	Anxa3	5	19.5	96.86	96.86	3.86	-0.02
ILMN_2980466	Idua	5	13.2	99.48	99.48	6.48	0.01
ILMN_1237581	0710007G10Rik	5	15.1	99.48	99.48	6.48	-0.03
ILMN_1238374	Cdc7	5	4.5	99.48	99.48	6.48	-0.05
ILMN_2866327	Pkd2	5	19.3	99.48	99.48	6.48	0.05
ILMN_2778112	Mapk10	5	10.0	99.48	99.48	6.48	-0.15
ILMN_2557762	C430014K22Rik	5	6.2	99.48	99.48	6.48	-0.02
ILMN_3009260	Coq2	5	10.4	99.48	99.48	6.48	-0.03
ILMN_1232659	C820017N15Rik	5	19.2	99.48	99.48	6.48	-0.05

Functional Genomic Architecture of Predisposition to Voluntary Exercise in Mice: Expression QTL in the Brain

Supporting Information for Kelly *et al*, 2012

Supporting Information

- **Supporting Information** - Files S1-S6 and Tables S1 and S2 (PDF, 214 KB)
- **Table S1** - Top correlations (partial, adjusted for sex and parent of origin) between exercise / body composition traits and transcript levels (PDF, 79 KB)
- **Table S2** - Candidate genes based on proximity to QTL for exercise and change in body weight/composition in response to exercise (PDF, 179 KB)
- **File S1** - Complete genotypes (.zip, 91 KB)
- **File S2** - Following Gordon et al. (2010), transcript expression profiles were normalized using Loess-Quantile normalization methods with R v 2.8.1 statistical software (R Development Core Team; www.r-project.com, lumi package) (.zip, 1 KB)
- **File S3** - Non-normalized and normalized transcript files (.zip, 141.9 MB)
- **File S4** - Non-normalized and normalized transcript files (.zip, 11.6 MB)
- **File S5** - Non-normalized and normalized transcript files (.zip, 11.8 MB)
- **File S6** - Non-normalized and normalized transcript files (.zip, 37 KB)