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**GENOME-WIDE SPERM DNA METHYLATION CHANGES AFTER THREE
MONTHS OF EXERCISE TRAINING IN HUMANS**

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26 **Abstract**

27 **Aim:** DNA methylation programs gene expression and is involved in numerous
28 biological processes. Accumulating evidence supports transgenerational inheritance
29 of DNA methylation changes in mammals via germ cells. Our aim was to determine
30 the effect of exercise on sperm DNA methylation.

31 **Materials and Methods:** Twenty-four men were recruited and assigned to an
32 exercise intervention or control group. Clinical parameters were measured and
33 sperm samples were donated by subjects before and after the three month time-
34 period. Mature sperm global and genome-wide DNA methylation was assessed
35 using an ELISA assay and the 450K BeadChip (Illumina).

36 **Results:** Global and genome-wide sperm DNA methylation was altered after three
37 months of exercise training. DNA methylation changes occurred in genes related to
38 numerous diseases such as Schizophrenia and Parkinson's disease.

39 **Conclusions:** Our study provides the first evidence showing exercise training
40 reprograms the sperm methylome. Whether these DNA methylation changes are
41 inherited to future generations warrants attention.

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51 **Executive summary**

52 *Aim*

- 53 • To determine the impact of exercise training on human sperm DNA
54 methylation.

55 *Materials and Methods*

- 56 • Twenty-four healthy young men were recruited and allocated to an exercise
57 training or control group.
- 58 • Health and fitness parameters were measured and sperm samples were
59 collected before and after three months.
- 60 • Global and genome-wide DNA methylation was quantified using an ELISA
61 assay and the Infinium HumanMethylation450 BeadChip (Illumina),
62 respectively.
- 63 • Significant alterations in CpG methylation and corresponding gene pathways
64 modulated by exercise training were analysed using Partek (Genomic Suite).
65 The disease association was performed using the Database for Annotation,
66 Visualization and Integrated Discovery (DAVID).

67 *Discussion*

- 68 • Exercise training was associated with global demethylation of human sperm.
- 69 • DNA methylation changes occurred across the genome after exercise
70 training in genes enriched for numerous developmental processes and
71 pathways associated with the adaptation to exercise training.
- 72 • Genes related to disease were methylated after exercise, indicating
73 transcriptional silencing.

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76 *Conclusions*

- 77 • We provide the first evidence demonstrating exercise training regulates the
78 human sperm methylome at CpG sites in genes associated with disease.

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80 **Introduction**

81 DNA methylation is crucial for long-term gene expression regulation [1, 2]. DNA
82 methylation is, however, reprogrammable through environmental conditions [3, 4].

83 Aberrant DNA methylation signatures are associated with age-related diseases such
84 as cancer [5-7], atherosclerosis [8, 9], type 2 diabetes mellitus [10, 11], Alzheimer's
85 disease [12] and major psychosis disorders [13, 14].

86 Mounting evidence indicates that environmentally induced DNA methylation changes
87 are inherited by subsequent generations and affects their phenotypes [15-22]. A
88 likely mechanism for inheritance of DNA methylation profile is via the germ cells.
89 Interestingly, aging is associated with sperm DNA methylation changes and may
90 influence disease risk of future generations [23, 24]. The differentially methylated
91 regions in sperm obtained from old (12–14 month-old) versus young (3-month-old)
92 mice were observed in the brain of the subsequent offspring, causing altered gene
93 expression and increased behaviors associated with psychiatric disorders
94 (schizophrenia and autism spectrum disorder) [24]. Although aging has been
95 investigated in context with sperm DNA methylation, the influence of other favorable
96 environmental stimuli are yet to be determined.

97 We recently found that exercise training significantly improves cardiorespiratory
98 fitness and lipid profile in conjunction with genome-wide leukocyte methylation
99 changes in young men [25]. Others have shown that exercise training modulates
100 skeletal myocyte [26-28] and adipocyte [29] DNA methylation as well as improving

101 health and fitness phenotypes. Thus, somatic cells are vulnerable to epigenetic
102 changes caused by exercise training, but whether exercise training regulates DNA
103 methylation in germ cells (oocyte or sperm) is currently unknown.
104 The aim of this study was to determine the impact of exercise training on human
105 sperm DNA methylation. Considering the mounting evidence supporting exercise
106 training as an environmental modulator of somatic cell DNA methylation [25-29], we
107 hypothesized that exercise training would significantly modify sperm DNA
108 methylation in genes related to human diseases.

109

110 **Materials and methods**

111 *Subjects*

112 Twenty-four healthy young men were recruited for this study. Subjects were non-
113 smoking, not taking any medications and free from any age-related chronic diseases,
114 according to self-administered health questionnaires. Subjects were eligible if they
115 had not engaged in any structured high-intensity aerobic exercise training during the
116 past six months and were recruited predominantly from the University by flyers and
117 by word-of-mouth.

118 The subjects' characteristics are outlined in Table 1. All subjects gave written
119 informed consent to participate and this study was approved by the Federation
120 University Australia Human Research Ethics Committee.

121 *Procedures*

122 On the initial day of testing, subjects were asked to complete health and physical
123 activity questionnaires in order to establish their eligibility to participate in the study.
124 Subjects were also familiarized with the testing procedures to follow and were given
125 a collection tube for their sperm donation.

126 The second testing session involved a sperm donation, blood donation, physical
127 measures and a test of maximal oxygen uptake ($\dot{V}O_{2max}$) on a treadmill. All testing
128 sessions were performed in the morning (7–10 AM). Height, weight and body mass
129 index were recorded using scales and a stadiometer. Blood pressure was measured
130 and augmentation index was assessed by non-invasive applanation tonometry using
131 the SphygmoCor instrument (AtCor, Australia). Subjects completed a maximal
132 treadmill exercise test to assess $\dot{V}O_{2max}$. After a three minute warm-up, subjects
133 began running at 10 km·h⁻¹ and the treadmill speed was progressively increased by 1
134 km·h⁻¹ every second minute until the volitional exhaustion or the supervising Exercise
135 Physiologist deemed it appropriate to stop the test. Participants were fitted with a
136 two-way breathing valve (Hans Rudolph) and breath-by-breath analysis was
137 performed by the online metabolic system (Moxus, Modular, USA). $\dot{V}O_{2max}$ was
138 determined as the highest O₂ value averaged over 60 s. Maximal treadmill speed
139 was deemed the highest speed successfully completed and was adjusted for time so
140 that participants were encouraged to exercise to their limit. The same testing
141 procedures were completed 3–5 days after the cases' final exercise session or three
142 months after their initial donation for controls.

143 *Sperm and blood processing*

144 Subjects gave resting preprandial sperm and blood donations before and after the
145 three month exercise intervention. Following an overnight fast, subjects extracted
146 their sperm by masturbating at home and donated their sample to the researchers at
147 the University within 30 min of extraction. All sperm donations and analyses were
148 performed according the World Health Organization's recommendations. Sperm cell
149 number and vitality was assessed by the same researcher using a sheep-counter.
150 Mature, motile sperm were isolated from lymphocytes, epithelial cells, immature or

151 abnormal sperm and other cellular debris using the PureSperm 40/80 reagents
152 (Nidacon). Briefly, 2 ml of PureSperm 40 was carefully layered on top of PureSperm
153 80, followed by gently aliquoting 1.5 ml of ejaculate onto the density gradient. The
154 density gradient was spun at 300 G for 20 min. The mature sperm were pelleted and
155 supernatant was removed. The pellet was washed twice by resuspending it in 5 ml of
156 PBS before being spun at 500 G for 10 min. DNA was extracted from mature sperm
157 suspended in 200 µl of PBS using the Purelink Genomic DNA Mini kit
158 (LifeTechnologies) following the manufacturer's recommendations with some small
159 adjustments. To deform the tightly packaged DNA in mature sperm, 0.03 mmol of
160 DL-Dithiothreitol solution (Sigma-Aldrich) was added to the sample before the
161 addition of proteinase K solution and the protein digestion step (incubation at 55°C)
162 was extended from the recommended 10 min to 90 min. All extractions were
163 performed immediately after sperm donation to prevent any temporal *de novo*
164 influences on DNA methylation. DNA yield was assessed using the Nanodrop 2000
165 Spectrophotometer (Thermo Scientific) before being stored at -20°C.
166 A preprandial blood sample (24 ml) was drawn from the antecubital vein into serum
167 separating tubes with the subject seated, using standard phlebotomy procedures.
168 Blood was immediately stored on ice before further processing. Blood lipid assays
169 were performed as described previously [25].

170 *Global DNA methylation analysis*

171 Average global DNA methylation of sperm from all subjects was quantified using the
172 5-mC ELISA Kit (Zymo Research, USA). All experiments were performed according
173 to the manufacturer's procedures. All paired samples before and after the
174 intervention were run on the same plate, as well as 100% methylated and 0%
175 methylated controls, all run in duplicate with a standard curve. Absorbance was

176 measured at 450 nm using the Multiskan FC Microplate Photometer (Thermo
177 Scientific, Australia) and average DNA methylation was calculated using the formula
178 generated from the standard curve. The average intra-assay coefficient of variation
179 for duplicate samples was 4.85%.

180 *Genome-wide DNA methylation analysis*

181 Genome-wide sperm DNA methylation was quantified in 12 cases before and after
182 the exercise intervention using the Infinium HumanMethylation 450K BeadChip
183 (Illumina) as previously described [25]. Experiments were conducted following the
184 manufacturer's guidelines, with the help of the Busselton Population Medical
185 Research Institute. Briefly, raw β -values underwent Subset-quantile Within Array
186 Normalization (SWAN) and were transformed to M-values using the logit function
187 ($\log^2(\beta/(1-\beta))$) before analyzing differentially methylated CpG sites after exercise
188 training. M-values were converted to β -values for representation of differentially
189 methylated CpG sites in tables and graphs because they correspond to the
190 percentage of CpG methylation and are a good biologically relevant representation.
191 Genome-wide DNA methylation data was analyzed using Partek (Genomic Suite,
192 version 6.6).

193 *Exercise training*

194 Subjects were randomly allocated to either an exercise training (cases) or control
195 group. Cases completed sprint interval training twice weekly for three months. Three
196 months of exercise training was chosen because it covered one human
197 spermatogenesis cycle. The controls did not engage in any form of training but were
198 asked not to deviate from their routine physical activity habits. All subjects were
199 asked to adhere to their normal diet. The sprint interval training schedule is outlined

200 in Table 2. Sprint interval training is an effective type of exercise training that rapidly
201 improves cardiorespiratory fitness and endurance performance [30-33].

202 The exercise training protocol of this study was based on research shown to improve
203 cardiorespiratory fitness and endurance performance [25, 34], but with some
204 adjustments, to avoid overuse injuries that could occur with an extended training
205 period (three months). Subjects completed 30 s sprints at maximal intensity with a
206 passive four minute rest period between efforts. Training began with three sprints
207 and was progressed by one effort every fortnight until week 7, when sprints were
208 kept at six efforts for the remaining six weeks of the intervention. Before each
209 session, subjects completed a short warm-up entailing a light 5 min jog, dynamic
210 stretches and some 20 m sprints at 70, 80, 90 and 100% of maximal effort. Training
211 was performed on the University's athletics oval and subjects were supervised and
212 given constant encouragement during sprints by an Exercise Physiologist.

213 *Statistical analyses*

214 Kolmogorov-Smirnov and Shapiro-Wilks were performed to assess normality. Two-
215 tailed paired *t*-tests were used to assess within-subject changes to physical, health
216 and fitness variables. A repeated measures ANOVA was used to determine the
217 interaction between global sperm DNA methylation before and after the intervention
218 in relation to cases and controls using IBM SPSS for Windows (version 21).

219 Differentially methylated CpG sites in cases were determined by repeated measures
220 ANOVA using Partek (Genomic Suite, version 6.6). In order to control for false
221 positives, a false discovery rate correction (FDR, $q \leq 0.1$) was applied to genome-wide
222 data by converting *p*-values to *q*-values. Hierarchical clustering, gene ontology and
223 pathway analysis on genome-wide CpG methylation data were performed using
224 Partek (Genomic Suite, version 6.6). Disease annotation analysis was conducted

225 using the Database for Annotation, Visualization and Integrated Discovery (DAVID,
226 version 6.7). Statistical significance was set at $p < 0.05$.

227

228 **Results**

229 *Exercise training improved cardiorespiratory fitness*

230 To determine whether exercise training alters human sperm DNA methylation, 13
231 untrained male volunteers completed three months of exercise training using a
232 modified training protocol (Table 2) previously shown to improve cardiorespiratory
233 fitness and induce genome-wide DNA methylation changes in leukocytes [25].

234 Although $\dot{V}O_{2\max}$ was unchanged (2.2%, $p=0.35$), relative to baseline, the cases, on
235 average, had a significantly lower resting heart rate by 10 beats·min⁻¹ and completed
236 an extra one min at a significantly higher maximal treadmill speed ($p=0.01$ and
237 $p=0.002$, respectively), while controls showed no significant changes in these
238 variables (Table 1).

239 To assess whether exercise training influences average sperm DNA methylation, we
240 assessed global sperm DNA methylation in cases and controls using ELISA-based
241 chemistry. After adjusting for ELISA plate, relative to the unchanged global sperm
242 DNA methylation observed in controls (n=11, 4.09%), sperm DNA was significantly
243 de-methylated after three months of exercise training (n=13, -6.63%, interaction
244 $p=0.006$) (Figure 1A and B).

245 Based on the global DNA methylation results we only quantified genome-wide sperm
246 DNA methylation in 12 cases before and after three months of exercise training
247 using the 450K BeadChip (Illumina). After applying a FDR ($q \leq 0.1$), we found DNA
248 methylation changes occurred throughout the genome in relation to the nearest gene
249 and CpG islands (Figure 1C and D). Of these, 7509 CpG sites relating to 4602

250 genes had significant DNA methylation changes ranging from 0.3 to 6.2% after
251 exercise training (Figure 1E and 2). More CpG sites were demethylated rather than
252 methylated after exercise training (4275 vs 3233, respectively). The top 25
253 methylated and demethylated CpG sites after exercise training are outlined in Table
254 3.

255 To gain insight into the biological impact of the CpG methylation changes following
256 exercise, we performed gene ontology and pathway analysis. Genes with altered
257 CpG methylation were those enriched for crucial biological processes including
258 developmental process, anatomical structure, embryonic morphogenesis and organ
259 development (Figure 3 and Supplementary Table 1). Pathway analysis revealed
260 genes with CpG site DNA methylation changes were enriched for pathways such as
261 MAPK signaling, PI3K-Akt signaling, pathways in cancer and ErbB signaling (Table
262 4).

263 In the search for the most biologically relevant CpG methylation changes, we
264 focused on CpG sites with a $\geq 1.5\%$ increase ($n=703$) or decrease ($n=1247$) in
265 methylation after exercise training and entered them into DAVID for disease
266 annotation analysis. While genes with demethylated CpG sites were those relating to
267 normal variation, those with increased methylation were enriched for numerous
268 diseases, with the most overrepresented diseases being Schizophrenia, Parkinson's
269 Disease, autism, cervical cancer and leukemia (Figure 4).

270 The global erasure of sperm CpG methylation that occurs after fertilization is well
271 established [35-37]. The sperm CpG methylation at imprinted genes, however, are
272 resistant to the global erasure after fertilization [38, 39] and as such, these genes are
273 key candidates for possible transgenerational inheritance through sperm. We found
274 16 paternally imprinted genes were differentially methylated after the three month

275 exercise training intervention (Table 5), in genes associated with pathologies
276 including EKG abnormalities (*KCNQ1OT1* and *KCNQ1*), autism and alcohol
277 dependence (*GABRG3*), Tourette syndrome, obsessive compulsive disorder and
278 dystonia (*SGCE*), and Alzheimer's disease, obesity, type 2 diabetes mellitus, blood
279 pressure and atherosclerosis (*IGF2* and *INS-IGF2*).

280

281 **Discussion**

282 Unlike the genome, the epigenome is malleable to changing environments and these
283 changes are somewhat heritable [3, 4]. Germ cells (sperm and oocytes) are likely
284 vectors that transfer environmentally-affected DNA methylation profiles to future
285 generations. We are the first to show the exercise training-induced DNA methylation
286 changes in human sperm. We found exercise training significantly manipulated
287 genome-wide DNA methylation and most strikingly, increased methylation in
288 disease-associated genes indicating transcriptional silencing. Moreover, methylation
289 changes occurred in paternally imprinted genes that are exempt from the DNA
290 methylation erasure after fertilization [38, 39].

291 Mounting evidence has demonstrated the capacity of exercise training to influence
292 the human DNA methylome in numerous tissues, including skeletal myocytes [26-
293 28], adipocytes [29] and leukocytes [25]. Exercise training or increased physical
294 activity tends to be associated with a reduced level of somatic cell global DNA
295 methylation. Leukocyte DNA methylation was anti-correlated to levels of physical
296 activity in 509 older adults (>70 y) [40] and we previously reported more
297 demethylated leukocyte CpG sites in response to a four week exercise training
298 intervention in young men [25]. Furthermore, global and gene-specific demethylation
299 occurred after acute exercise in human skeletal myocytes [41]. In the present study,

300 we found global sperm DNA methylation was reduced after three months of exercise
301 training, suggesting that exercise may systemically demethylate both somatic and
302 germ cells. Interestingly, older adults have more heavily methylated global sperm
303 DNA compared to their younger counterparts [23, 42]. Also defective human sperm
304 exhibit nearly two-fold higher levels of global DNA methylation [43]. To that end, the
305 global demethylation observed in our subjects after exercise training could be
306 favorable, possibly counteracting the increased DNA methylation associated with
307 ageing. This, in turn, could positively influence fertility though future studies are
308 necessary.

309 Interestingly, exercise training was associated with sperm methylation changes to
310 CpG sites in genes related to pathways and biological processes similar to those
311 observed in skeletal muscle [26] and leukocytes [25] from previous studies. For
312 example, pathways regulated by exercise training-induced leukocyte DNA
313 methylation alterations [25] that were also observed in sperm include MAPK
314 signaling, PI3K-Akt signaling and pathways in cancer. Similarly, overlapping
315 pathways between skeletal muscle [26] and sperm pathways modulated by exercise
316 training include MAPK signaling, insulin signaling and ErbB signaling. Therefore, it
317 would seem that some exercise-responsive genes (CpG sites) are regulated by DNA
318 methylation in human somatic cells and also in sperm.

319 The genes with CpG methylation changes in the present study were enriched for
320 numerous molecular and cellular processes including anatomical structure
321 development and morphogenesis, single-organism development and embryonic
322 morphogenesis. Genes with exercise-induced CpG methylation changes were also
323 associated with many debilitating diseases such as Schizophrenia, Parkinson's
324 disease, cervical cancer, leukemia and autism. The genes associated with diseases

325 were methylated after exercise training, indicating that these genes may have been
326 transcriptionally silenced. Age-associated sperm CpG methylation patterns were
327 observed in genes implicated in Schizophrenia in humans [23] and mice [24]. Some
328 of the adverse DNA methylation patterns found in sperm of aged mice was
329 transmitted to the brain of their offspring, leading to transcriptional dysregulation of
330 genes involved in schizophrenia and autism, facilitating the disease-related traits
331 [24]. Furthermore, offspring (F1 to F3) of gestating female rats treated with endocrine
332 disruptors (bisphenol-A, bis[2-ethylhexyl]phthalate and dibutyl phthalate and
333 vinclozolin) have altered sperm DNA methylation and an increased risk of testis
334 disease, obesity and infertility [15, 44, 45]. These environmentally-induced DNA
335 methylation aberrations led to transcriptional changes in common pathways across
336 numerous somatic cells, including those regulated in the present study (MAPK
337 signaling, insulin signaling and pathways in cancer) [46]. Whether the altered sperm
338 DNA methylation observed in our subjects will be transmitted to their offspring and
339 prevent the development of disease is speculative and would require large human
340 studies involving the analysis of multiple generations.

341 Germ cells undergo global demethylation following fertilization [35, 39].
342 Consequently, the likelihood of such CpG methylation changes surviving this
343 demethylation event is uncertain. We did, however, reveal a number of paternally
344 imprinted genes (e.g. *IGF2*, *INS-IGF2*, *SGCE* and *GABRG3*) had differentially
345 methylated CpGs after exercise training. These genes are exempt from the global
346 demethylation after fertilization [38, 39] and as such, are key candidates for exercise-
347 induced transgenerational inheritance of DNA methylation gene programming. Our
348 disease analysis using DAVID revealed the differentially methylated paternally
349 imprinted genes after exercise training were related to neurological disorders

350 (autism, Alzheimer's disease, Tourette's syndrome and obsessive compulsive
351 disorder) and cardio-metabolic diseases (obesity, type 2 diabetes mellitus, high
352 blood pressure and atherosclerosis). Whilst no evidence exists, it is tempting to
353 speculate that exercise training may remodel the sperm methylome and that this
354 epigenetic modification may reduce the disease risk of offspring.

355 DNA methyltransferase enzymes (DNMT1, DNMT3A, DNMT3B and DNMT3L) as
356 well as ten-eleven translocation (TET1, TET2 and TET3) proteins could be
357 modulated by exercise training leading to altered DNA methylation. Our study was
358 not designed to target the exact physiological or molecular mechanism by which
359 exercise training influences DNA methylation in sperm, rather it was designed to
360 investigate whether exercise training influences sperm DNA methylation. Therefore,
361 further research is required to identify the molecular mechanisms evoking the
362 changes in the sperm methylome after exercise training.

363 Our study has several limitations. Firstly, our study had a modest sample size and
364 there was a statistically different global sperm DNA methylation between cases and
365 controls at baseline. While we acknowledge this is not desirable, our statistical
366 analysis accounted for the observed difference. We do, however, recommend that
367 our results should be verified in a larger population. The relative exercise workload
368 was not standardized. We did, however, ask that all subjects perform each sprint
369 maximally without pacing to ensure they are working at maximal intensity. Certain
370 diets are associated with DNA methylation levels in somatic cells [47, 48]. Despite
371 asking our subjects not to deviate from their routine dietary habits, the lack of control
372 for diet in our study should also be acknowledged. Finally, we did not control for
373 genotype-DNA methylation interactions or quantify DNA methylation in context with
374 other epigenetic modifications or gene expression. Nonetheless, our novel finding

375 that exercise alters human sperm DNA methylation should encourage future
376 investigations into the influence of exercise training on germ cell epigenetic
377 modifications and gene regulation.

378

379 **Conclusions**

380 We report for the first time that exercise training significantly modifies the human
381 sperm methylome. Whilst exercise training was associated with an increased global
382 sperm demethylation overall, methylation in key genes associated with human
383 disease was increased indicating transcriptional silencing of these genes.

384

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527

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534 **Competing interests**

535 The authors have no competing interests to disclose.

536

537 **Figure Legends**

538 **Figure 1. Sperm DNA methylation changes after exercise training.** Average
539 percent (\pm SE) of global sperm DNA methylation is given for 13 cases (A) and 11
540 controls (B) after the three month intervention. Relative to the controls who showed
541 no global methylation change, cases exhibited a global demethylation (-6.63%) after
542 three months of exercise training (mean \pm SE: 39.1 \pm 3.85 to 43.2 \pm 3.6 and 52.95 \pm 3.56
543 to 46.3 \pm 3.4, respectively, interaction $p=0.006$). Data are from repeated measures
544 ANOVA adjusting for ELISA plate number. Genome-wide DNA methylation changes
545 at CpG sites in relation to the nearest gene (C) and CpG islands (D) are shown. Data
546 are from Chi² tests. E) The number of CpG sites with increased methylation (black
547 bars) and decreased methylation (grey bars) are given on the y-axis with the

548 magnitude of change illustrated on the x-axis. Data are from differentially methylated
549 CpG sites ($q \leq 0.1$).

550 **Figure 2. Hierarchical clustering of CpG sites after three months of exercise**
551 **training.** The CpG methylation status is indicated by blue (low methylation) and
552 yellow (high methylation) from 12 subjects before (grey bar) and after (purple bar)
553 three months of exercise training. Each branch of the array tree on the left of the
554 purple and grey bars are subjects. The array tree at the top of the hierarchical cluster
555 indicates clusters of CpG sites modified by exercise training. Data are from
556 differentially methylated CpG sites ($q \leq 0.1$).

557 **Figure 3. Gene ontology for genes with differentially methylated CpG sites**
558 **after exercise training.** Genes with altered CpG site methylation after exercise are
559 grouped for function on the y-axis with corresponding enrichment scores on the x-
560 axis. Data are from differentially methylated CpG sites ($q \leq 0.1$).

561 **Figure 4. Disease annotation analysis for genes with differentially methylated**
562 **CpG sites after exercise training.** Data are from genes with a $\geq 1.5\%$ increase or
563 decrease in methylation after exercise training ($q \leq 0.1$). The y-axis represents the
564 number of genes for each annotated disease (x-axis).

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Table 1. Participant characteristics before and after three months of exercise training.

Variable	Cases (n=13)		Controls (n=11)	
	Before	After	Before	After
	Exercise	Exercise		
Age (y)	24.4±5.19		22.45±4.74	
Ht (cm)	181.1±6.54		177.95±4.07	
Wt (kg)	83.58±10.7	84.01±11.97	82.22±11.83	82.93±10.64
BMI (Wt/Ht ²)	25.53±3.34	25.89±3.61	25.94±3.5	25.9±3.08
HR (beats·min ⁻¹)	78.54±15.64	68.23±7.15*	68.18±11.58	66.45±8.19
SBP (mm Hg)	130.46±11.82	129.85±10.64	123.45±9.2	123.09±10.24
DBP (mm Hg)	77.23±9.87	76.38±7.85	75.82±8.51	72.27±7.14
CSBP (mm Hg)	110.92±9.86	111.08±8.43	106.91±8.38	105.72±9.32
CDBP (mm Hg)	76.08±17.35	77.69±7.77	76.36±8.64	73.64±7.38
Aix (%)	-4.15±9.73	-4.15±8.73	-2.36±12.8	-1.18±11.71
Cholesterol (mmol/l) [^]	4.82±0.88	4.77±1.04	4.01±1.0	3.97±0.77
Triglyceride (mmol/l) [^]	1.01±0.48	1.07±0.46	0.9±0.38	0.82±0.18
HDLC (mmol/l) [^]	1.43±0.25	1.43±0.3	1.37±0.2	1.29±0.14
LDLC (mmol/l) [^]	2.92±0.79	2.87±0.88	2.22±0.75	2.32±0.74
Glucose (mmol/l) [^]	4.78±0.38	5.22±0.52	4.9±0.46	4.92±0.31
Insulin (mmol/l) [^]	6.94±2.72	10.72±6.44	7.15±3.65	12.78±16.42
$\dot{V}O_{2max}$ (ml·kg ⁻¹ ·min ⁻¹)	47.43±5.64	48.47±6.0	45.85±7.34	44.92±5.49
Maximal treadmill speed (km·h ⁻¹)	14.4±1.12	14.9±1.11**	14.07±1.52	13.84±1.8
Sperm volume (ml)	4.7±1.4	5.17±0.87	3.95±1.7	3.97±1.79 ²⁴

Sperm #	1.35×10 ⁹ ±	1.39×10 ⁹ ±	1.58×10 ⁹ ±	1.33×10 ⁹ ±
	1.21×10 ⁹	1.41×10 ⁹	1.56×10 ⁹	1.39×10 ⁹
Sperm alive (n)	9.12×10 ⁸ ±	9.08×10 ⁸ ±	8.36×10 ⁸ ±	6.05×10 ⁸ ±
	1.09×10 ⁹	1.02×10 ⁹	1.07×10 ⁹	4.68×10 ⁸
Sperm alive (%)	61.65±24.42	62.72±13.77	48.26±23.26	53.89±14.14

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572 Legend: Ht, height; Wt, weight; BMI, body mass index; HR, resting heart rate; SBP,
573 systolic blood pressure; DBP, diastolic blood pressure; CSBP, central (aortic) blood
574 pressure; CDBP, central (aortic) diastolic blood pressure; augmentation index;
575 HDLC, high-density lipo-protein cholesterol; LDLC, low-density lipoprotein
576 cholesterol; $\dot{V}O_{2max}$, maximal oxygen uptake; ^, n=8; #, number; %, percentage. Data
577 are from two-tailed paired t-test and expressed as mean±SD. Sperm analysis was
578 conducted on semen samples and not from highly motile sperm isolated using the
579 PureSperm 40/80 reagents (Nidacon).

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592 Table 2. Description of the three month exercise program.

Week	Session #	Training load*	Training sprint time (min)	Total session time (min)
1	1	3 sprints	1.5	9.5
	2	3 sprints	1.5	9.5
2	3	3 sprints	1.5	9.5
	4	3 sprints	1.5	9.5
3	5	4 sprints	2	14
	6	4 sprints	2	14
4	7	4 sprints	2	14
	8	4 sprints	2	14
5	9	5 sprints	2.5	18.5
	10	5 sprints	2.5	18.5
6	11	5 sprints	2.5	18.5
	12	5 sprints	2.5	18.5
7	13	6 sprints	3	23
	14	6 sprints	3	23
8	15	6 sprints	3	23
	16	6 sprints	3	23
9	17	6 sprints	3	23
	18	6 sprints	3	23
10	19	6 sprints	3	23
	20	6 sprints	3	23
11	21	6 sprints	3	23
	22	6 sprints	3	23
12	23	6 sprints	3	23
	24	6 sprints	3	23

Total Time

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593 Legend: # number; * all sprints were completed at maximum intensity, separated by a four
594 minute passive recovery.

595 Table 3. DNA methylation changes after three months of exercise training ($q \leq 0.1$).

<i>Location in relation to</i>					<i>DNA methylation (%)</i>				
CpG site	Closest gene	Gene region	CpG island	Chr	Before (mean±SD)	After exercise (mean±SD)	Δ	p-value	q-value (≤0.1)
cg02598618	-	-	Open sea	10	94.0±1.4	98.6±1.1	4.6	1.79×10 ⁻⁵	0.06
cg02655397	-	-	N shelf	11	80.7±4.4	85.1±3.3	4.5	0.0005	0.08
cg10243075	<i>CACNA1A</i>	Body	N shore	19	23.2±3.6	27.6±5.0	4.4	0.0004	0.08
cg27222157	<i>RBM14</i>	TSS1500	N shore	11	22.2±6.8	26.5±8.5	4.4	0.0009	0.08
cg10413297	<i>RFPL3S</i>	TSS1500	Open sea	22	25.6±6.7	29.7±6.6	4.1	0.001	0.09
cg16533336	<i>WBSCR17</i>	Body	Open sea	7	76.7±2.6	80.8±2.3	4.1	1.17×10 ⁻⁷	0.02
cg09194930	<i>MT1L</i>	TSS200	Island	16	14.7±9.5	18.8±12.7	4.1	0.001	0.09

cg00685853	-	-	N shore	2	14.4±3.9	18.4±6.2	4.0	0.0001	0.07
cg27205941	<i>GMDS</i>	TSS200	Island	6	29.0±4.1	32.9±3.5	4.0	0.001	0.09
cg17745251	<i>C10orf140</i>	Body	Island	10	25.0±2.7	29.0±3.0	4.0	0.002	0.09
cg25485435	<i>RAMP1</i>	TSS1500	N shore	2	16.9±3.5	20.8±3.0	3.9	0.0002	0.07
cg11888420	-	-	Open	6	33.0±2.7	36.8±4.6	3.8	0.001	0.09
			sea						
cg08715827	-	-	Open	12	6.1±2.3	9.8±5.8	3.8	0.001	0.09
			sea						
cg15617548	<i>GORASP2</i>	5'UTR	Island	2	23.5±2.8	27.1±2.8	3.7	0.0009	0.08
		1stExon							
cg15488194	<i>MBNL1</i>	TSS1500	Open	3	23.9±11.9	27.5±12.8	3.7	0.002	0.097
		5'UTR	sea						
cg17271592	<i>HIST2H2AA4</i>	TSS1500	Island	1	13.8±3.1	17.4±2.6	3.6	0.0006	0.08
	<i>HIST2H2AA3</i>								
cg06785129	<i>RFPL3</i>	TSS1500	Open	22	18.6±3.2	22.2±4.2	3.6	0.002	0.09
			sea						

cg14047339	<i>RUNX2</i>	Body	Island	6	33.7±2.2	37.3±2.9	3.6	0.002	0.09
		5'UTR							
	<i>SUPT3H</i>	1stExon							
		5'UTR							
cg13916261	<i>FNBP1</i>	Body	N shelf	9	24.4±3.9	27.9±4.9	3.5	0.0003	0.08
cg09303484	-	-	Open	7	63.3±4.3	66.8±3.6	3.5	0.0008	0.08
			sea						
cg05528975	-	-	Open	2	25.9±2.5	29.4±3.1	3.5	0.0005	0.08
			sea						
cg17627829	<i>HCG18</i>	Body	N shore	6	9.5±3.4	13.0±4.1	3.5	0.002	0.09
cg05629323	<i>TFDP3</i>	3'UTR	Open	X	8.8±2.7	12.3±4.4	3.5	0.002	0.09
		1stExon	sea						
cg20681184	<i>PIK3CD</i>	5'UTR	S shore	1	14.5±2.8	18.0±4.5	3.5	0.002	0.09
cg15069995	<i>HORMAD1</i>	5'UTR	Open	1	5.9±2.1	9.3±3.9	3.4	0.0009	0.08
			sea						
cg13062455	<i>SEL1L</i>	Body	Open	14	88.2±2.3	85.4±3.3	-2.9	1.27×10 ⁻⁵	0.05

			sea						
cg24360197	-	-	Open	15	70.1±8.4	67.2±7.9	-2.9	0.001	0.09
			sea						
cg03359503	<i>CLIC2</i>	5'UTR	Open	X	87.7±4.1	84.7±5	-3.0	0.0009	0.08
		1 st Exon	sea						
cg24121979	-	-	Open	12	94.9±3.2	91.9±2.0	-3.0	0.0003	0.08
			sea						
cg20909579	<i>PDE6B</i>	TSS1500	Island	4	89.6±2.9	86.6±5.4	-3.0	0.0008	0.08
		Body							
cg02507663	<i>NCRNA00219</i>	Body	S shore	5	54.9±8.4	51.9±8.4	-3.0	0.001	0.09
	<i>SNORA13</i>	TSS200							
cg27569203	<i>CELSR1</i>	Body	Island	22	90.2±2.4	87.3±1.6	-3.0	0.002	0.09
cg26235273	<i>DKK3</i>	3'UTR	Open	11	71.0±4.0	67.8±3.8	-3.1	0.0006	0.08
			sea						
cg17518550	<i>C1orf150</i>	TSS200	Open	1	82.3±4.0	79.2±6.4	-3.1	0.001	0.09
			sea						

cg16514287	<i>SLC25A36</i>	Body	Open	3	94.0±1.4	90.8±1.1	-3.1	1.7×10 ⁻⁶	0.03
			sea						
cg26057840†	-	-	N shore	20	89.4±2.7	86.2±2.6	-3.2	0.0005	0.08
cg24544876	-	-	S shore	5	78.3±3.3	75.1±2.5	-3.2	0.0008	0.08
cg14630692	<i>URM1</i>	Body	Open	9	86.4±1.7	83.2±2.4	-3.2	0.001	0.09
			sea						
cg03440485	-	-	Island	X	22.9±2.3	19.7±2.1	-3.2	0.001	0.09
cg15832577‡	<i>C1orf53</i>	Body	S shore	1	78.6±2.5	75.3±3.2	-3.3	0.0002	0.07
cg17494438	<i>DRGX</i>	TSS1500	N shelf	10	82.6±1.8	79.2±2.8	-3.3	0.001	0.09
cg16320838	<i>DNAJB7</i>	TSS1500	Open	22	92.5±14.5	89.0±19.1	-3.5	0.0005	0.08
	<i>XPNPEP3</i>	Body	sea						
cg11342670	<i>KIAA0319</i>	Body	Open	6	78.9±9.3	75.5±10.3	-3.5	0.001	0.09
			sea						
cg03987985	<i>L1TD1</i>	3'UTR	Open	1	75.6±4.6	72.0±5.6	-3.6	0.001	0.09
			sea						
cg08377570	<i>LPAR6</i>	TSS1500	Open	13	87.5±2.1	83.8±2.5	-3.7	0.0005	0.07

	<i>RB1</i>	Body	sea							596
cg17486639	-	-	N shelf	19	89.8±1.6	86.0±3.1	-3.8	0.0006	0.08	597
cg03834767	<i>CDK14</i>	3'UTR	Open	7	90.6±2.0	86.4±6.0	-4.1	0.002	0.09	598
			sea							599
cg16631698	-	-	Island	10	81.7±4.2	77.2±2.3	-4.5	0.002	0.09	600
cg08269188	<i>CBX5</i>	5'UTR	Open	12	83.7±2.7	79.0±4.5	-4.7	5.17×10 ⁻⁵	0.06	601
			sea							602
cg05946920	<i>GGA1</i>	Body	Island	22	39.7±6.7	33.6±3.4	-6.2	0.002	0.09	603
										604

605 Data are expressed as beta values ± standard deviation.

606 Legend: Chr, chromosome number; Δ, difference; 3', three prime; 5', five prime; UTR, untranslated region; TSS1500, 1500 bases

607 upstream of transcription start site; TSS200, 200 bases upstream of transcription start site; *DMR, differentially methylated region;

608 †CDMR, cancer differentially methylated region; ‡RDMR, reprogrammed differentially methylated region.

609 Table 4. Molecular pathways related to genes with differentially methylated CpG
 610 sites after exercise training ($p \leq 0.05$).

Pathway Name	Enrichment Score	p-value	# genes	Pathway ID
Circadian entrainment	8.0	0.0003	24	kegg pathway 51
Axon guidance	7.2	0.001	29	kegg pathway 176
Endocytosis	7.0	0.001	39	kegg pathway 211
Glutamatergic synapse	6.1	0.002	25	kegg pathway 182
Protein digestion and absorption	5.9	0.003	22	kegg pathway 46
ECM-receptor interaction	5.4	0.004	19	kegg pathway 41
GABAergic synapse	4.7	0.01	22	kegg pathway 133
Bile secretion	4.4	0.01	18	kegg pathway 74
MAPK signaling pathway	4.4	0.01	41	kegg pathway 119
Focal adhesion	4.3	0.01	34	kegg pathway 5
PI3K-Akt signaling pathway	4.3	0.01	54	kegg pathway 45
Huntington's disease	4.3	0.01	33	kegg pathway 53
Transcriptional misregulation in cancer	4.3	0.01	31	kegg pathway 94
African trypanosomiasis	4.1	0.02	10	kegg pathway 69
Colorectal cancer	4.1	0.02	13	kegg pathway 148
Viral myocarditis	3.9	0.02	15	kegg pathway 105
Taurine and hypotaurine metabolism	3.7	0.02	4	kegg pathway 195
Galactose metabolism	3.7	0.03	8	kegg pathway 15

Long-term depression	3.6	0.03	12	kegg pathway 250
Endocrine and other factor- regulated calcium reabsorption	3.6	0.03	10	kegg pathway 258
Retrograde endocannabinoid signaling	3.6	0.03	21	kegg pathway 129
Glycosaminoglycan biosynthesis - chondroitin sulfate / dermatan sulfate	3.4	0.03	7	kegg pathway 248
Nicotine addiction	3.4	0.03	10	kegg pathway 62
Allograft rejection	3.4	0.03	10	kegg pathway 177
Selenocompound metabolism	3.4	0.04	5	kegg pathway 135
Morphine addiction	3.2	0.04	20	kegg pathway 86
Amoebiasis	3.2	0.04	21	kegg pathway 56
Graft-versus-host disease	3.1	0.04	10	kegg pathway 209
Maturity onset diabetes of the young	3.1	0.04	7	kegg pathway 241
Pathways in cancer	3.1	0.05	49	kegg pathway 128
ErbB signaling pathway	3.1	0.05	15	kegg pathway 121
Type I diabetes mellitus	2.9	0.05	10	kegg pathway 242
Insulin secretion	2.9	0.05	17	kegg pathway 4

611 Table 5. Paternally imprinted gene CpG methylation changes caused by exercise training.

<i>Location in relation to</i>					<i>DNA methylation (%)</i>				
Paternally imprinted gene	CpG site	Gene region	CpG island	Chr	Basal (mean±SD)	After exercise (mean±SD)	Δ	p-value	q-value (≤0.1)
<i>GRB10</i>	cg12358041	5'UTR Body	Open sea	7	92.3±1.2	91.0±1.2	-1.3	0.0004	0.08
	cg26050906	5'UTR TSS200	Open sea	7	91.8±1.1	90.9±1.1	-0.9	0.003	0.10
<i>SGCE</i>	cg22090863*	Body TSS1500	N shore	7	4.0±0.6	4.6±0.6	0.7	0.0007	0.08
<i>PEG10</i>									
<i>SGCE</i>	cg18139769	TSS1500 5'UTR	S shore	7	10.5±2.0	13.5±4.5	3.0	0.0006	0.08
<i>PEG10</i>									
<i>DLGAP2</i>	cg27316067	Body	S shore	8	64.3±11.2	62.2±11.3	-2.1	0.002	0.09
<i>SFMBT2</i>	cg15362304	Body	S shelf	10	93.4±1.1	92.5±1.1	-0.9	0.0007	0.08
<i>INS-IGF2</i>	cg00273464	Body	Open sea	11	89.8±1.7	87.7±1.2	-2.0	0.00002	0.06

<i>IGF2</i>		1stExon								
		5'UTR								
<i>INS-IGF2</i>	cg17665927	Body	Open sea	11	93.2±1.3	91.6±1.4	-1.5	0.0002	0.07	
<i>IGF2</i>		1stExon								
		5'UTR								
<i>INS-IGF2</i>	cg05384664	Body	S shore	11	88.6±2.2	87.3±2.8	-1.4	0.001	0.09	
<i>IGF2</i>		Body								
<i>KCNQ1OT1</i>	cg20406758‡	Body	Open sea	11	95.5±1.0	94.1±1.0	-1.4	0.001	0.09	
<i>KCNQ1</i>		Body								
<i>SLC38A4</i>	cg12152384	Body	Open sea	12	93.4±1.0	92.3±0.9	-1.1	0.002	0.09	
<i>WIF1</i>	cg15862358	TSS1500	S shore	12	6.7±2.6	8.6±5.5	1.9	0.001	0.09	
<i>DLK1</i>	cg17412258	TSS1500	CpG island	14	2.0±0.5	2.8±0.6	0.8	0.0005	0.08	
	cg06504820	TSS1500	N shore	14	21.5±6.7	24.1±7.6	2.5	0.0003	0.07	
<i>RTL1</i>	cg23546343	1stExon	N shore	14	93.0±0.9	91.8±1.0	-1.2	0.002	0.10	
<i>MIR431</i>		TSS200								
<i>MIR433</i>		TSS1500								
<i>GABRG3</i>	cg08325929	Body	S shelf	15	86.2±2.5	84.9±2.7	-1.3	0.003	0.10	

<i>ZIM2</i>	cg16008476	Body	N shore	19	5.9±1.6	7.6±2.7	1.7	0.0006	0.08
<i>HM13</i>	cg06000530	Body	CpG island	20	4.0±1.0	5.6±2.2	1.6	0.002	0.10
<i>PSIMCT-1</i>		TSS200							

612 Data are expressed are beta values ± standard deviation.

613 Legend: Chr, chromosome number; Δ, difference; 3', three prime; 5', five prime; UTR, untranslated region; TSS1500, 1500 bases upstream of
614 transcription start site; TSS200, 200 bases upstream of transcription start site; *DMR, differentially methylated region; ‡RDMR, reprogrammed
615 differentially methylated region.

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626 Supplementary Table 1. Gene ontology for genes with DNA methylation changes after exercise training ($q \leq 0.1$).

Function	Type	Enrichment score	p-value	q-value	# genes	Go ID
Single-organism process	BP	34.82	7.57×10^{-16}	3.88×10^{-12}	1428	44699
Single-organism cellular process	BP	26.32	3.70×10^{-12}	9.50×10^{-9}	1251	44763
Biological process	BP	23.74	4.89×10^{-11}	8.22×10^{-8}	1968	8150
Cellular process	BP	23.47	6.41×10^{-11}	8.22×10^{-8}	1678	9987
Developmental process	BP	21.96	2.89×10^{-10}	2.97×10^{-7}	591	32502
Biological regulation	BP	19.53	3.31×10^{-9}	2.83×10^{-6}	1227	65007
Regulation of biological process	BP	18.66	7.88×10^{-9}	5.78×10^{-6}	1168	50789
Anatomical structure development	BP	18.31	1.12×10^{-8}	7.18×10^{-6}	374	48856
Anatomical structure morphogenesis	BP	17.79	1.87×10^{-8}	1.07×10^{-5}	213	9653

Cellular developmental process	BP	17.46	2.62×10^{-8}	1.29×10^{-5}	312	48869
Regulation of cellular process	BP	17.38	2.84×10^{-8}	1.29×10^{-5}	1113	50794
Single-organism developmental process	BP	17.32	3.01×10^{-8}	1.29×10^{-5}	405	44767
Ras guanyl-nucleotide exchange factor activity	MF	17.22	3.32×10^{-8}	1.31×10^{-5}	36	5088
Guanyl-nucleotide exchange factor activity	MF	17.04	3.97×10^{-8}	1.45×10^{-5}	50	5085
Gtpase regulator activity	MF	15.96	1.18×10^{-7}	4.02×10^{-5}	96	30695
Sequence-specific DNA binding transcription factor activity	MF	15.66	1.58×10^{-7}	4.68×10^{-5}	182	3700
Pattern specification process	BP	15.65	1.60×10^{-7}	4.68×10^{-5}	84	7389
Nucleic acid binding	MF	15.52	1.81×10^{-7}	4.68×10^{-5}	182	1071

transcription factor						
activity						
Small gtpase regulator	MF	15.52	1.82×10^{-7}	4.68×10^{-5}	71	5083
activity						
Ion binding	MF	15.49	1.88×10^{-7}	4.68×10^{-5}	867	43167
Nucleoside-	MF	15.47	1.91×10^{-7}	4.68×10^{-5}	97	60589
triphosphatase regulator						
activity						
Multicellular organismal	BP	14.95	3.22×10^{-7}	7.51×10^{-5}	435	32501
process						
Embryonic	BP	14.90	3.37×10^{-7}	7.51×10^{-5}	81	48598
morphogenesis						
Single-multicellular	BP	14.75	3.91×10^{-7}	8.37×10^{-5}	428	44707
organism process						
Molecular function	MF	14.47	5.18×10^{-7}	0.0001	2015	3674
Regulation of cell	BP	14.16	7.09×10^{-7}	0.0001	319	10646
communication						

Regulation of signaling	BP	14.14	7.22×10^{-7}	0.0001	318	23051
Regulation of cell development	BP	13.86	9.59×10^{-7}	0.0002	124	60284
Cell junction	CC	13.47	1.42×10^{-6}	0.0003	136	30054
Sequence-specific DNA binding	MF	13.17	1.90×10^{-6}	0.0003	127	43565
Binding	MF	12.88	2.55×10^{-6}	0.0004	1597	5488
Cell differentiation	BP	12.46	3.88×10^{-6}	0.0006	218	30154
Regulation of neurogenesis	BP	12.44	3.96×10^{-6}	0.0006	80	50767
Regionalization	BP	12.19	5.08×10^{-6}	0.0008	53	3002
Regulation of nervous system development	BP	12.16	5.24×10^{-6}	0.0008	87	51960
Negative regulation of cell differentiation	BP	11.75	7.85×10^{-6}	0.001	88	45596
Cellular response to stimulus	BP	11.54	9.69×10^{-6}	0.001	653	51716

Extracellular matrix	CC	11.31	1.22×10^{-5}	0.002	65	31012
Regulation of neuron differentiation	BP	11.27	1.28×10^{-5}	0.002	67	45664
Motor activity	MF	11.21	1.35×10^{-5}	0.002	34	3774
Extracellular matrix part	CC	11.21	1.35×10^{-5}	0.002	44	44420
Organ development	BP	11.20	1.37×10^{-5}	0.002	159	48513
Positive regulation of cellular process	BP	11.08	1.55×10^{-5}	0.002	471	48522
Regulation of cell differentiation	BP	10.78	2.08×10^{-5}	0.002	174	45595
Negative regulation of developmental process	BP	10.76	2.12×10^{-5}	0.002	103	51093
Positive regulation of cellular biosynthetic process	BP	10.76	2.13×10^{-5}	0.002	210	31328
Dendritic spine	CC	10.73	2.19×10^{-5}	0.002	18	43197
Synaptic transmission	BP	10.72	2.22×10^{-5}	0.002	81	7268

Neuron part	CC	10.65	2.36×10^{-5}	0.002	105	97458
System development	BP	10.60	2.50×10^{-5}	0.003	115	48731
Response to external stimulus	BP	10.57	2.57×10^{-5}	0.003	168	9605
Synapse part	CC	10.35	3.21×10^{-5}	0.003	71	44456
Cell communication	BP	10.34	3.22×10^{-5}	0.003	148	7154
Signal transduction	BP	10.33	3.26×10^{-5}	0.003	538	7165
Axon guidance	BP	10.31	3.32×10^{-5}	0.003	68	7411
Negative regulation of neuron differentiation	BP	10.15	3.91×10^{-5}	0.003	18	45665
Neuron spine	CC	10.15	3.91×10^{-5}	0.003	18	44309
Cation binding	MF	10.14	3.94×10^{-5}	0.003	581	43169
Metal ion binding	MF	10.07	4.23×10^{-5}	0.004	572	46872
Positive regulation of biosynthetic process	BP	10.06	4.26×10^{-5}	0.004	211	9891
Positive regulation of macromolecule	BP	10.05	4.33×10^{-5}	0.004	196	10557

biosynthetic process						
Regulation of signal transduction	BP	10.04	4.38×10^{-5}	0.004	271	9966
Phospholipid binding	MF	9.97	4.66×10^{-5}	0.004	93	5543
Ion channel activity	MF	9.89	5.05×10^{-5}	0.004	73	5216
Anterior/posterior pattern specification	BP	9.83	5.40×10^{-5}	0.004	36	9952
Substrate-specific channel activity	MF	9.68	6.24×10^{-5}	0.005	74	22838
Rho guanyl-nucleotide exchange factor activity	MF	9.61	6.69×10^{-5}	0.005	22	5089
Negative regulation of signal transduction	BP	9.56	7.04×10^{-5}	0.005	110	9968
Cell part	CC	9.55	7.10×10^{-5}	0.005	1907	44464
Negative regulation of response to stimulus	BP	9.48	7.66×10^{-5}	0.006	131	48585
Positive regulation of	BP	9.45	7.84×10^{-5}	0.006	194	45935

nucleobase-containing compound metabolic process						
Regulation of axon extension involved in axon guidance	BP	9.42	8.13×10^{-5}	0.006	7	48841
Negative regulation of biological process	BP	9.26	9.50×10^{-5}	0.007	456	48519
Regulation of small gtpase mediated signal transduction	BP	9.26	9.55×10^{-5}	0.007	56	51056
Regulation of purine nucleotide metabolic process	BP	9.24	9.69×10^{-5}	0.007	72	1900542
Cell development	BP	9.12	0.0001	0.007	79	48468
Negative regulation of cell communication	BP	9.04	0.0001	0.008	114	10648

Gated channel activity	MF	9.03	0.0001	0.008	60	22836
Ion gated channel activity	MF	9.03	0.0001	0.008	60	22839
DNA binding	MF	9.00	0.0001	0.008	351	3677
Response to stimulus	BP	8.99	0.0001	0.008	827	50896
Positive regulation of nitrogen compound metabolic process	BP	8.94	0.0001	0.008	196	51173
Regulation of nucleotide metabolic process	BP	8.91	0.0001	0.008	72	6140
Channel activity	MF	8.88	0.0001	0.008	76	15267
Passive transmembrane transporter activity	MF	8.88	0.0001	0.008	76	22803
Organ morphogenesis	BP	8.80	0.0002	0.009	76	9887
Extracellular matrix disassembly	BP	8.78	0.0002	0.009	22	22617
Negative regulation of	BP	8.74	0.0002	0.009	113	23057

signaling						
Negative regulation of cellular process	BP	8.67	0.0002	0.01	421	48523
Neuron projection	CC	8.64	0.0002	0.01	80	43005
Cell projection part	CC	8.61	0.0002	0.01	111	44463
Positive regulation of cellular metabolic process	BP	8.61	0.0002	0.01	292	31325
Positive regulation of RNA metabolic process	BP	8.52	0.0002	0.01	173	51254
Regulation of cellular component organization	BP	8.51	0.0002	0.01	202	51128
Intracellular part	CC	8.51	0.0002	0.01	1607	44424
Enzyme regulator activity	MF	8.51	0.0002	0.01	161	30234
Positive regulation of metabolic process	BP	8.48	0.0002	0.01	306	9893

Regulation of Ras protein signal transduction	BP	8.45	0.0002	0.01	35	46578
Regulation of multicellular organismal process	BP	8.45	0.0002	0.01	275	51239
Cation channel activity	MF	8.40	0.0002	0.01	54	5261
Negative regulation of canonical Wnt receptor signaling pathway	BP	8.39	0.0002	0.01	22	90090
Collagen metabolic process	BP	8.39	0.0002	0.01	22	32963
Plasma membrane part	CC	8.38	0.0002	0.01	284	44459
Collagen	CC	8.37	0.0002	0.01	24	5581
Locomotion	BP	8.34	0.0002	0.01	159	40011
Regulation of multicellular organismal	BP	8.27	0.0003	0.01	178	2000026

development						
Regulation of Wnt	BP	8.25	0.0003	0.01	40	30111
receptor signaling						
pathway						
Collagen catabolic	BP	8.25	0.0003	0.01	20	30574
process						
Multicellular organismal	BP	8.20	0.0003	0.01	24	44236
metabolic process						
Regulation of	BP	8.14	0.0003	0.01	214	32879
localization						
Connective tissue	BP	8.08	0.0003	0.01	26	61448
development						
Positive regulation of	BP	8.07	0.0003	0.01	164	45893
transcription, DNA-						
dependent						
Positive regulation of	BP	8.06	0.0003	0.01	34	43547
gtpase activity						

Positive regulation of macromolecule metabolic process	BP	7.97	0.0003	0.02	284	10604
Neuron fate commitment	BP	7.96	0.0004	0.02	11	48663
Ionotropic glutamate receptor complex	CC	7.96	0.0004	0.02	11	8328
Synaptic membrane	CC	7.95	0.0004	0.02	45	97060
Multicellular organismal catabolic process	BP	7.93	0.0004	0.02	21	44243
Ion transmembrane transporter activity	MF	7.90	0.0004	0.02	127	15075
Cellular component organization	BP	7.86	0.0004	0.02	491	16043
Establishment of localization	BP	7.84	0.0004	0.02	427	51234
Embryonic placenta development	BP	7.84	0.0004	0.02	10	1892

Localization	BP	7.84	0.0004	0.02	71	51179
Tissue development	BP	7.83	0.0004	0.02	96	9888
Regulation of canonical Wnt receptor signaling pathway	BP	7.68	0.0005	0.02	30	60828
Energy reserve metabolic process	BP	7.67	0.0005	0.02	32	6112
Regulation of cellular component biogenesis	BP	7.67	0.0005	0.02	68	44087
Membrane-bounded vesicle	CC	7.66	0.0005	0.02	104	31988
Intracellular signal transduction	BP	7.65	0.0005	0.02	206	35556
Regulation of Rho protein signal transduction	BP	7.59	0.0005	0.02	23	35023
Axis specification	BP	7.52	0.0005	0.02	18	9798

Ion channel complex	CC	7.50	0.0006	0.02	41	34702
Microtubule motor activity	MF	7.48	0.0006	0.02	20	3777
Signaling	BP	7.46	0.0006	0.02	118	23052
Single organism signaling	BP	7.46	0.0006	0.02	118	44700
Negative regulation of Wnt receptor signaling pathway	BP	7.44	0.0006	0.02	27	30178
Embryonic organ morphogenesis	BP	7.44	0.0006	0.02	27	48562
Cell-cell signaling	BP	7.44	0.0006	0.02	115	7267
Positive regulation of gene expression	BP	7.39	0.0006	0.02	174	10628
Multicellular organismal macromolecule metabolic process	BP	7.32	0.0007	0.02	22	44259

Establishment or maintenance of cell polarity	BP	7.32	0.0007	0.02	22	7163
Regulation of developmental growth	BP	7.32	0.0007	0.02	26	48638
Lipid binding	MF	7.30	0.0007	0.02	123	8289
Regulation of cell proliferation	BP	7.29	0.0007	0.02	183	42127
Substrate-specific transmembrane transporter activity	MF	7.22	0.0007	0.03	134	22891
Regulation of developmental process	BP	7.21	0.0007	0.03	223	50793
Taxis	BP	7.16	0.0008	0.03	92	42330
Chemotaxis	BP	7.16	0.0008	0.03	92	6935
Ligand-gated ion channel activity	MF	7.15	0.0008	0.03	30	15276

Ligand-gated channel activity	MF	7.15	0.0008	0.03	30	22834
Cell fate determination	BP	7.15	0.0008	0.03	13	1709
Vesicle	CC	7.13	0.0008	0.03	116	31982
Negative regulation of cell development	BP	7.02	0.0009	0.03	27	10721
Wnt receptor signaling pathway	BP	7.02	0.0009	0.03	44	16055
Cellular component organization or biogenesis	BP	7.02	0.0009	0.03	491	71840
Positive regulation of biological process	BP	7.00	0.0009	0.03	513	48518
Membrane	CC	6.94	0.0010	0.03	801	16020
Regulation of metabolic process	BP	6.92	0.0010	0.03	672	19222
Positive regulation of	BP	6.90	0.0010	0.03	118	45944

transcription from RNA polymerase II promoter						
Negative regulation of axonogenesis	BP	6.90	0.0010	0.03	13	50771
Regulation of respiratory gaseous exchange	BP	6.89	0.0010	0.03	8	43576
Transport	BP	6.87	0.0010	0.03	416	6810
Transport vesicle membrane	CC	6.86	0.0011	0.03	17	30658
Energy derivation by oxidation of organic compounds	BP	6.85	0.0011	0.03	37	15980
Positive regulation of cell development	BP	6.84	0.0011	0.03	33	10720
Regulation of cell adhesion	BP	6.82	0.0011	0.03	51	30155
Actin filament-based	BP	6.82	0.0011	0.03	54	30029

process						
Cell surface receptor	BP	6.81	0.0011	0.03	312	7166
signaling pathway						
Cell-cell junction	CC	6.79	0.0011	0.03	52	5911
Activation of Ras gtpase	BP	6.79	0.0011	0.03	10	32856
activity						
Chromatin binding	MF	6.73	0.0012	0.04	62	3682
Tissue morphogenesis	BP	6.72	0.0012	0.04	63	48729
Regulation of	BP	6.70	0.0012	0.04	487	19219
nucleobase-containing						
compound metabolic						
process						
Negative regulation of	BP	6.69	0.0012	0.04	22	50768
neurogenesis						
Microtubule associated	CC	6.64	0.0013	0.04	29	5875
complex						
Transcription, DNA-	BP	6.59	0.0014	0.04	308	6351

dependent						
Early endosome	CC	6.57	0.0014	0.04	21	31901
membrane						
Cation channel complex	CC	6.52	0.0015	0.04	29	34703
Positive regulation of	BP	6.49	0.0015	0.04	26	50769
neurogenesis						
Coated vesicle	CC	6.49	0.0015	0.04	25	30662
membrane						
Columnar/cuboidal	BP	6.42	0.0016	0.05	7	2066
epithelial cell						
development						
Regulation of steroid	BP	6.42	0.0016	0.05	13	50810
biosynthetic process						
ER to Golgi transport	CC	6.42	0.0016	0.05	11	12507
vesicle membrane						
Dynein complex	CC	6.40	0.0017	0.05	12	30286
Positive regulation of	BP	6.40	0.0017	0.05	88	51130

cellular component

organization

Site of polarized growth	CC	6.39	0.0017	0.05	22	30427
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Skeletal system	BP	6.37	0.0017	0.05	23	48705
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morphogenesis

Negative regulation of	BP	6.37	0.0017	0.05	23	10741
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intracellular protein

kinase cascade

Common myeloid	BP	6.33	0.0018	0.05	3	35726
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progenitor cell

proliferation

Regulation of	BP	6.33	0.0018	0.05	3	14807
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somitogenesis

Detection of	BP	6.33	0.0018	0.05	3	34287
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monosaccharide

stimulus

Detection of glucose	BP	6.33	0.0018	0.05	3	51594
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Detection of carbohydrate stimulus	BP	6.33	0.0018	0.05	3	9730
Detection of hexose stimulus	BP	6.33	0.0018	0.05	3	9732
Insulin-like growth factor-activated receptor activity	MF	6.33	0.0018	0.05	3	5010
Laminin-10 complex	CC	6.33	0.0018	0.05	3	43259
Cell projection	CC	6.26	0.0019	0.05	139	42995
Multicellular organismal development	BP	6.25	0.0019	0.05	81	7275
Positive regulation of Ras gtpase activity	BP	6.23	0.0020	0.05	23	32320
Endoplasmic reticulum part	CC	6.22	0.0020	0.05	142	44432
Regulation of GTP catabolic process	BP	6.21	0.0020	0.05	44	33124

Regulation of nitrogen compound metabolic process	BP	6.20	0.0020	0.05	495	51171
Neuron recognition	BP	6.19	0.0020	0.05	10	8038
Negative regulation of cell proliferation	BP	6.17	0.0021	0.05	88	8285
Regulation of cellular metabolic process	BP	6.16	0.0021	0.05	612	31323
Negative regulation of axon extension involved in axon guidance	BP	6.14	0.0022	0.05	5	48843
Negative regulation of JAK-STAT cascade	BP	6.14	0.0022	0.05	5	46426
N-methyl-D-aspartate selective glutamate receptor complex	CC	6.14	0.0022	0.05	5	17146
Regulation of	BP	6.10	0.0022	0.05	22	50770

axonogenesis

Neuron differentiation	BP	6.09	0.0023	0.06	38	30182
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Cytoskeleton	BP	6.05	0.0024	0.06	93	7010
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organization

Regulation of growth	BP	6.05	0.0024	0.06	85	40008
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Regulation of	BP	6.01	0.0025	0.06	48	9118
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nucleoside metabolic

process

Establishment of protein	BP	5.98	0.0025	0.06	9	90150
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localization to

membrane

Integral to endoplasmic	CC	5.97	0.0025	0.06	21	30176
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reticulum membrane

Growth cone	CC	5.97	0.0025	0.06	21	30426
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Cartilage development	BP	5.97	0.0025	0.06	6	60351
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involved in

endochondral bone

morphogenesis						
Enzyme linked receptor	BP	5.96	0.0026	0.06	112	7167
protein signaling						
pathway						
Intramembraneous	BP	5.93	0.0027	0.06	4	1957
ossification						
Direct ossification	BP	5.93	0.0027	0.06	4	36072
Regulation of transport	BP	5.91	0.0027	0.06	157	51049
Embryonic skeletal	BP	5.90	0.0027	0.06	18	48704
system morphogenesis						
Regulation of catabolic	BP	5.90	0.0027	0.06	88	9894
process						
Regulation of gtpase	BP	5.90	0.0027	0.06	43	43087
activity						
Transmembrane	BP	5.90	0.0028	0.06	87	7169
receptor protein tyrosine						
kinase signaling						

pathway						
Extracellular vesicular exosome	CC	5.85	0.0029	0.07	16	70062
Antigen processing and presentation of exogenous peptide antigen via MHC class II	BP	5.83	0.0029	0.07	21	19886
Tight junction	CC	5.83	0.0029	0.07	23	5923
Occluding junction	CC	5.83	0.0029	0.07	23	70160
Serine-type endopeptidase inhibitor activity	MF	5.83	0.0029	0.07	22	4867
Cellular component movement	BP	5.83	0.0029	0.07	138	6928
Membrane-enclosed lumen	CC	5.78	0.0031	0.07	101	31974
Vesicle membrane	CC	5.77	0.0031	0.07	61	12506

Regulatory region nucleic acid binding	MF	5.77	0.0031	0.07	62	1067
Regulatory region DNA binding	MF	5.77	0.0031	0.07	62	975
Regulation of primary metabolic process	BP	5.76	0.0031	0.07	601	80090
Regulation of purine nucleotide catabolic process	BP	5.72	0.0033	0.07	47	33121
Cartilage development	BP	5.72	0.0033	0.07	19	51216
Response to glucagon stimulus	BP	5.71	0.0033	0.07	12	33762
Regulation of anatomical structure morphogenesis	BP	5.70	0.0034	0.07	98	22603
Cytoplasmic vesicle membrane	CC	5.65	0.0035	0.07	59	30659

Regulation of biological quality	BP	5.65	0.0035	0.07	314	65008
Regulation of nucleotide catabolic process	BP	5.64	0.0035	0.07	47	30811
Metal ion transmembrane transporter activity	MF	5.64	0.0036	0.08	65	46873
Ionotropic glutamate receptor activity	MF	5.62	0.0036	0.08	7	4970
Cell motility	BP	5.60	0.0037	0.08	102	48870
Regulation of stress- activated MAPK cascade	BP	5.60	0.0037	0.08	31	32872
Single-organism transport	BP	5.59	0.0037	0.08	323	44765
Regulation of cellular localization	BP	5.58	0.0038	0.08	111	60341

Antigen processing and presentation of peptide antigen via MHC class II	BP	5.56	0.0038	0.08	21	2495
Response to endogenous stimulus	BP	5.56	0.0039	0.08	156	9719
Actin cytoskeleton organization	BP	5.55	0.0039	0.08	44	30036
Anchoring collagen	CC	5.55	0.0039	0.08	5	30934
Axonal growth cone	CC	5.55	0.0039	0.08	5	44295
Mannose metabolic process	BP	5.55	0.0039	0.08	5	6013
Semaphorin-plexin signaling pathway	BP	5.52	0.0040	0.08	6	71526
Biological adhesion	BP	5.52	0.0040	0.08	121	22610
Cell adhesion	BP	5.52	0.0040	0.08	121	7155
Extracellular organelle	CC	5.51	0.0040	0.08	16	43230
Extracellular membrane-	CC	5.51	0.0040	0.08	16	65010

bounded organelle						
Regulation of stress-activated protein kinase signaling cascade	BP	5.50	0.0041	0.08	31	70302
Positive regulation of insulin secretion	BP	5.50	0.0041	0.08	12	32024
Macromolecule localization	BP	5.47	0.0042	0.08	57	33036
Intrinsic to endoplasmic reticulum membrane	CC	5.46	0.0043	0.08	23	31227
Homeostatic process	BP	5.45	0.0043	0.08	152	42592
Transmembrane transporter activity	MF	5.44	0.0043	0.08	141	22857
Endocytosis	BP	5.44	0.0044	0.08	46	6897
Negative regulation of cell adhesion	BP	5.43	0.0044	0.08	20	7162
Integral to luminal side	CC	5.41	0.0045	0.09	9	71556

of endoplasmic reticulum membrane						
Embryonic skeletal system development	BP	5.41	0.0045	0.09	10	48706
Protein binding	MF	5.40	0.0045	0.09	965	5515
Small gtpase mediated signal transduction	BP	5.36	0.0047	0.09	71	7264
Regulation of steroid metabolic process	BP	5.35	0.0047	0.09	16	19218
Secretion by cell	BP	5.33	0.0048	0.09	63	32940
Liver development	BP	5.32	0.0049	0.09	17	1889
Antigen processing and presentation of peptide or polysaccharide antigen via MHC class II	BP	5.30	0.0050	0.09	21	2504
Epithelial tube morphogenesis	BP	5.29	0.0050	0.09	19	60562

Regulation of response to stimulus	BP	5.28	0.0051	0.09	348	48583
Gtpase activator activity	MF	5.27	0.0051	0.09	47	5096
Organelle	CC	5.27	0.0051	0.09	1126	43226
Extracellular-glutamate- gated ion channel activity	MF	5.27	0.0051	0.09	7	5234
Osteoblast development	BP	5.27	0.0051	0.09	7	2076
Adherens junction	CC	5.25	0.0053	0.10	37	5912
Cardiac septum morphogenesis	BP	5.22	0.0054	0.10	11	60411
Cation transmembrane transporter activity	MF	5.22	0.0054	0.10	94	8324
Secretion	BP	5.22	0.0054	0.10	75	46903
Regulation of insulin secretion	BP	5.21	0.0054	0.10	29	50796
Regulation of peptide	BP	5.21	0.0055	0.10	31	90276

hormone secretion						
Regulation of hormone secretion	BP	5.19	0.0056	0.10	36	46883
Dorsal spinal cord development	BP	5.19	0.0056	0.10	4	21516
Peripheral nervous system myelin maintenance	BP	5.19	0.0056	0.10	4	32287
Positive regulation of superoxide anion generation	BP	5.19	0.0056	0.10	4	32930
Lipid particle organization	BP	5.19	0.0056	0.10	4	34389
Morphogenesis of an epithelium	BP	5.17	0.0057	0.10	50	2009
Positive regulation of hormone secretion	BP	5.17	0.0057	0.10	17	46887

Establishment of protein localization to plasma membrane	BP	5.17	0.0057	0.10	8	90002
Rab guanyl-nucleotide exchange factor activity	MF	5.17	0.0057	0.10	8	17112
Negative regulation of osteoblast differentiation	BP	5.17	0.0057	0.10	10	45668
Response to chemical stimulus	BP	5.16	0.0057	0.10	366	42221
Ras gtpase activator activity	MF	5.16	0.0057	0.10	25	5099
Response to nitrogen compound	BP	5.15	0.0058	0.10	96	1901698
Axonogenesis	BP	5.13	0.0059	0.10	24	7409
Regulation of JNK cascade	BP	5.13	0.0059	0.10	27	46328
Substrate-specific	MF	5.12	0.0059	0.10	146	22892

transporter activity						
Positive regulation of	BP	5.12	0.0060	0.10	81	45597
cell differentiation						
Cytoplasmic membrane-	CC	5.11	0.0060	0.10	89	16023
bounded vesicle						
RNA biosynthetic	BP	5.11	0.0061	0.10	323	32774
process						
Regulation of secretion	BP	5.10	0.0061	0.10	74	51046
Regulation of cell-	BP	5.10	0.0061	0.10	23	10810
substrate adhesion						
Neuropeptide receptor	MF	5.10	0.0061	0.10	12	8188
activity						
Establishment of cell	BP	5.10	0.0061	0.10	12	30010
polarity						
Cellular component	BP	5.09	0.0061	0.10	63	32989
morphogenesis						
Cell fate commitment	BP	5.09	0.0062	0.10	26	45165

Positive regulation of secretion	BP	5.09	0.0062	0.10	40	51047
Golgi apparatus part	CC	5.07	0.0063	0.10	103	44431
Response to organic nitrogen	BP	5.05	0.0064	0.10	92	10243
Regulation of sequestering of triglyceride	BP	5.05	0.0064	0.10	5	10889
Platelet-derived growth factor binding	MF	5.05	0.0064	0.10	5	48407
MHC class II receptor activity	MF	5.05	0.0064	0.10	5	32395
Positive regulation of neuron differentiation	BP	5.04	0.0065	0.10	16	45666
Small conductance calcium-activated potassium channel	MF	5.04	0.0065	0.10	3	16286

activity						
Cardiac endothelial cell	BP	5.04	0.0065	0.10	3	3348
differentiation						
Endocardial cell	BP	5.04	0.0065	0.10	3	60956
differentiation						
N-acetylgalactosaminyl- proteoglycan 3-beta- glucuronosyltransferase activity	MF	5.04	0.0065	0.10	3	50510
Positive regulation of transcription of Notch receptor target	BP	5.04	0.0065	0.10	3	7221
Glossopharyngeal nerve morphogenesis	BP	5.04	0.0065	0.10	3	21615
Extracellular matrix-cell signaling	BP	5.04	0.0065	0.10	3	35426
Immunoglobulin	BP	5.04	0.0065	0.10	3	2381

production involved in
immunoglobulin
mediated immune
response

Nerve growth factor	BP	5.04	0.0065	0.10	3	32455
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processing

Enzyme binding	MF	5.04	0.0065	0.10	162	19899
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Cell recognition	BP	5.03	0.0066	0.10	17	8037
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Regulation of peptide	BP	5.02	0.0066	0.10	31	2791
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secretion

Regulation of peptide	BP	5.02	0.0066	0.10	31	90087
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transport

Cytoplasmic vesicle part	CC	4.99	0.0068	0.10	73	44433
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Skeletal system	BP	4.97	0.0069	0.11	30	1501
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development

Postsynaptic membrane	CC	4.97	0.0070	0.11	35	45211
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Postsynaptic density	CC	4.96	0.0070	0.11	22	14069
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Bone morphogenesis	BP	4.95	0.0071	0.11	7	60349
Synaptic transmission, glutamatergic	BP	4.95	0.0071	0.11	7	35249
Cortical actin cytoskeleton	CC	4.95	0.0071	0.11	7	30864
Cellular response to glucagon stimulus	BP	4.95	0.0071	0.11	10	71377
Negative regulation of growth	BP	4.94	0.0071	0.11	36	45926
Regulation of transcription from RNA polymerase II promoter	BP	4.92	0.0073	0.11	185	6357
Embryonic digit morphogenesis	BP	4.91	0.0074	0.11	12	42733
Regulation of extent of cell growth	BP	4.91	0.0074	0.11	12	61387
Potassium channel	CC	4.90	0.0075	0.11	16	34705

complex						
Voltage-gated	CC	4.90	0.0075	0.11	16	8076
potassium channel						
complex						
Regulation of JAK-STAT	BP	4.90	0.0075	0.11	16	46425
cascade						
Regulation of	BP	4.88	0.0076	0.11	186	51174
phosphorus metabolic						
process						
Gland development	BP	4.84	0.0079	0.12	22	48732
Anion binding	MF	4.84	0.0079	0.12	380	43168
Regulation of	BP	4.83	0.0080	0.12	34	42391
membrane potential						
Regulation of phosphate	BP	4.81	0.0081	0.12	184	19220
metabolic process						
Epithelial cell	BP	4.80	0.0082	0.12	24	2064
development						

Embryonic heart tube morphogenesis	BP	4.79	0.0083	0.12	14	3143
Inner ear morphogenesis	BP	4.79	0.0083	0.12	14	42472
Regulation of vesicle-mediated transport	BP	4.79	0.0084	0.12	40	60627
Clathrin-coated vesicle membrane	CC	4.77	0.0085	0.12	19	30665
Cell migration	BP	4.77	0.0085	0.12	91	16477
Central nervous system neuron differentiation	BP	4.77	0.0085	0.12	15	21953
Negative regulation of axon extension	BP	4.75	0.0086	0.12	6	30517
Protein kinase C activity	MF	4.75	0.0086	0.12	6	4697
Regulation of cellular catabolic process	BP	4.75	0.0086	0.12	75	31329
Response to growth	BP	4.75	0.0086	0.12	83	70848

factor stimulus						
Organic substance	BP	4.75	0.0087	0.12	500	1901576
biosynthetic process						
L-amino acid	MF	4.73	0.0088	0.12	10	15179
transmembrane						
transporter activity						
Embryo implantation	BP	4.73	0.0088	0.12	10	7566
Endocytic vesicle	CC	4.73	0.0088	0.12	22	30666
membrane						
Glycogen metabolic	BP	4.73	0.0088	0.12	12	5977
process						
Transcription-coupled	BP	4.73	0.0088	0.12	12	6283
nucleotide-excision						
repair						
Neuron projection	BP	4.72	0.0089	0.12	32	48812
morphogenesis						
Epidermis development	BP	4.69	0.0092	0.13	28	8544

Regulation of actin filament-based process	BP	4.68	0.0093	0.13	37	32970
Cellular response to growth factor stimulus	BP	4.68	0.0093	0.13	81	71363
Response to nicotine	BP	4.67	0.0094	0.13	9	35094
Midbrain development	BP	4.67	0.0094	0.13	9	30901
Cell body	CC	4.67	0.0094	0.13	44	44297
Positive regulation of peptide hormone secretion	BP	4.67	0.0094	0.13	13	90277
G-protein coupled receptor signaling pathway	BP	4.67	0.0094	0.13	84	7186
Cellular nitrogen compound biosynthetic process	BP	4.66	0.0095	0.13	366	44271
Pancreas development	BP	4.65	0.0095	0.13	7	31016

Ventricular septum morphogenesis	BP	4.65	0.0095	0.13	7	60412
Protein localization	BP	4.65	0.0096	0.13	51	8104
Regulation of actin cytoskeleton organization	BP	4.64	0.0096	0.13	35	32956
Regulation of cyclic nucleotide metabolic process	BP	4.64	0.0096	0.13	25	30799
Binding, bridging	MF	4.64	0.0097	0.13	27	60090
Neuronal cell body	CC	4.64	0.0097	0.13	40	43025
Canonical Wnt receptor signaling pathway	BP	4.62	0.0099	0.13	17	60070
Atrial septum morphogenesis	BP	4.61	0.0099	0.13	5	60413
Outer membrane- bounded periplasmic	CC	4.61	0.0099	0.13	5	30288

space

Periplasmic space	CC	4.61	0.0099	0.13	5	42597
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Detection of bacterium	BP	4.61	0.0099	0.13	5	16045
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Endocytic recycling	BP	4.61	0.0099	0.13	5	32456
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Microtubule	CC	4.61	0.01	0.13	58	5874
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Positive regulation of	BP	4.61	0.01	0.13	79	51050
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transport

Hepatocyte	BP	4.59	0.01	0.13	4	70365
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differentiation

Glomerular visceral	BP	4.59	0.01	0.13	4	72015
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epithelial cell

development

Hydrogen peroxide	BP	4.59	0.01	0.13	4	50665
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biosynthetic process

RNA-induced silencing	CC	4.59	0.01	0.13	4	16442
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complex

Rnai effector complex	CC	4.59	0.01	0.13	4	31332
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Regulation of dendritic cell antigen processing and presentation	BP	4.59	0.01	0.13	4	2604
Left/right axis specification	BP	4.59	0.01	0.13	4	70986
CARD domain binding	MF	4.59	0.01	0.13	4	50700
Neuron migration	BP	4.59	0.01	0.13	21	1764
Cellular localization	BP	4.59	0.01	0.13	49	51641
Regulation of cell morphogenesis involved in differentiation	BP	4.59	0.01	0.13	34	10769
Regulation of cellular component movement	BP	4.58	0.01	0.13	73	51270
Glucan metabolic process	BP	4.55	0.01	0.13	12	44042
Cellular glucan metabolic process	BP	4.55	0.01	0.13	12	6073

Brain development	BP	4.55	0.01	0.13	32	7420
Transcription regulatory region DNA binding	MF	4.55	0.01	0.13	58	44212
Cell proliferation	BP	4.55	0.01	0.13	88	8283
Regulation of interleukin-1 beta production	BP	4.53	0.01	0.13	10	32651
Biosynthetic process	BP	4.52	0.01	0.13	507	9058
Cytoplasmic vesicle	CC	4.51	0.01	0.14	97	31410
Positive regulation of peptide secretion	BP	4.51	0.01	0.14	13	2793
Positive regulation of cytokine biosynthetic process	BP	4.49	0.01	0.14	14	42108
Appendage morphogenesis	BP	4.48	0.01	0.14	21	35107
Limb morphogenesis	BP	4.48	0.01	0.14	21	35108

Embryonic forelimb morphogenesis	BP	4.45	0.01	0.14	9	35115
Tight junction assembly	BP	4.45	0.01	0.14	9	70830
Positive regulation of cell adhesion	BP	4.45	0.01	0.14	25	45785
Cellular response to acid	BP	4.44	0.01	0.14	11	71229
Golgi membrane	CC	4.43	0.01	0.14	80	139
Asymmetric protein localization	BP	4.42	0.01	0.14	6	8105
Positive regulation of developmental process	BP	4.42	0.01	0.14	106	51094
Neuron development	BP	4.41	0.01	0.15	22	48666
Potassium channel activity	MF	4.41	0.01	0.15	22	5267
Regulation of camp metabolic process	BP	4.41	0.01	0.15	22	30814

Cytoplasmic part	CC	4.40	0.01	0.15	888	44444
Intrinsic to plasma membrane	CC	4.40	0.01	0.15	156	31226
Coated vesicle	CC	4.40	0.01	0.15	26	30135
Clathrin-coated vesicle	CC	4.40	0.01	0.15	24	30136
Negative regulation of developmental growth	BP	4.40	0.01	0.15	8	48640
Insulin-like growth factor binding	MF	4.40	0.01	0.15	8	5520
Regulation of locomotion	BP	4.39	0.01	0.15	73	40012
Intracellular organelle	CC	4.39	0.01	0.15	1114	43229
Cellular response to vascular endothelial growth factor stimulus	BP	4.38	0.01	0.15	7	35924
Positive regulation of epithelial to	BP	4.38	0.01	0.15	7	10718

mesenchymal transition						
DNA-dependent	BP	4.37	0.01	0.15	38	6352
transcription, initiation						
Calcium channel activity	MF	4.37	0.01	0.15	21	5262
Lung development	BP	4.36	0.01	0.15	17	30324
Regulation of	BP	4.34	0.01	0.15	14	14013
gliogenesis						
Regulation of axon	BP	4.34	0.01	0.15	10	30516
extension						
Positive regulation of	BP	4.34	0.01	0.15	10	31281
cyclase activity						
Aromatic compound	BP	4.34	0.01	0.15	355	19438
biosynthetic process						
Organic cyclic	BP	4.32	0.01	0.15	370	1901362
compound biosynthetic						
process						
Organelle lumen	CC	4.32	0.01	0.15	90	43233

Cellular_component	CC	4.30	0.01	0.15	2166	5575
Aminoglycan metabolic process	BP	4.30	0.01	0.15	29	6022
Digestive tract development	BP	4.27	0.01	0.16	11	48565
Cortical cytoskeleton	CC	4.27	0.01	0.16	11	30863
Inorganic cation transmembrane transporter activity	MF	4.26	0.01	0.16	74	22890
Anterior/posterior axis specification	BP	4.25	0.01	0.16	9	9948
Cytoskeleton	CC	4.23	0.01	0.16	106	5856
Cellular membrane organization	BP	4.23	0.01	0.16	64	16044
Plasma membrane	CC	4.23	0.01	0.16	488	5886
Dopaminergic neuron differentiation	BP	4.23	0.01	0.16	5	71542

Regulation of respiratory gaseous exchange by neurological system process	BP	4.23	0.01	0.16	5	2087
Positive regulation of Wnt receptor signaling pathway	BP	4.22	0.01	0.16	16	30177
Phosphoglucomutase activity	MF	4.22	0.01	0.16	3	4614
Microvillus assembly	BP	4.22	0.01	0.16	3	30033
Microvillus organization	BP	4.22	0.01	0.16	3	32528
Noradrenergic neuron differentiation	BP	4.22	0.01	0.16	3	3357
Positive regulation of Wnt receptor signaling pathway, planar cell polarity pathway	BP	4.22	0.01	0.16	3	2000096

Response to oleic acid	BP	4.22	0.01	0.16	3	34201
Chemorepellent activity	MF	4.22	0.01	0.16	3	45499
Positive regulation of steroid hormone biosynthetic process	BP	4.22	0.01	0.16	3	90031
Membrane-bounded organelle	CC	4.19	0.02	0.17	1000	43227
Generation of precursor metabolites and energy	BP	4.17	0.02	0.17	63	6091
Non-canonical Wnt receptor signaling pathway	BP	4.17	0.02	0.17	8	35567
Microtubule-based movement	BP	4.16	0.02	0.17	28	7018
Heterocycle biosynthetic process	BP	4.16	0.02	0.17	354	18130
Nucleobase-containing	BP	4.15	0.02	0.17	345	34654

compound biosynthetic process						
Glycogen biosynthetic process	BP	4.13	0.02	0.17	6	5978
Glucan biosynthetic process	BP	4.13	0.02	0.17	6	9250
Cell differentiation in hindbrain	BP	4.13	0.02	0.17	6	21533
MHC class II protein complex	CC	4.13	0.02	0.17	6	42613
Regulation of timing of cell differentiation	BP	4.11	0.02	0.17	4	48505
Glomerular epithelial cell development	BP	4.11	0.02	0.17	4	72310
Negative regulation of catenin import into nucleus	BP	4.11	0.02	0.17	4	35414

Negative regulation of smooth muscle cell differentiation	BP	4.11	0.02	0.17	4	51151
Pinocytosis	BP	4.11	0.02	0.17	4	6907
Semaphorin receptor activity	MF	4.11	0.02	0.17	4	17154
RNA polymerase II core binding	MF	4.11	0.02	0.17	4	993
Regulation of glial cell differentiation	BP	4.10	0.02	0.17	11	45685
Regulation of stem cell proliferation	BP	4.10	0.02	0.18	16	72091
Extracellular matrix organization	BP	4.09	0.02	0.18	43	30198
Regulation of DNA binding	BP	4.08	0.02	0.18	15	51101
Organic cyclic	MF	4.07	0.02	0.18	721	97159

compound binding						
Regulation of	BP	4.07	0.02	0.18	12	32642
chemokine production						
Phagocytic vesicle	CC	4.07	0.02	0.18	12	30670
membrane						
Palate development	BP	4.06	0.02	0.18	14	60021
Regulation of cyclase	BP	4.06	0.02	0.18	14	31279
activity						
Cellular biosynthetic	BP	4.06	0.02	0.18	482	44249
process						
Positive regulation of	BP	4.05	0.02	0.18	9	14015
gliogenesis						
Tissue homeostasis	BP	4.04	0.02	0.18	18	1894
Regulation of cell	BP	4.03	0.02	0.18	44	31344
projection organization						
Extracellular structure	BP	4.02	0.02	0.18	43	43062
organization						

Actin binding	MF	4.01	0.02	0.19	58	3779
Endosome membrane	CC	4.00	0.02	0.19	51	10008
Regulation of cell growth	BP	3.98	0.02	0.19	48	1558
Positive regulation of lyase activity	BP	3.98	0.02	0.19	10	51349
Response to fatty acid	BP	3.98	0.02	0.19	10	70542
Regulation of epithelial to mesenchymal transition	BP	3.98	0.02	0.19	10	10717
Tube morphogenesis	BP	3.97	0.02	0.19	19	35239
Macromolecule biosynthetic process	BP	3.97	0.02	0.19	384	9059
Embryo development ending in birth or egg hatching	BP	3.97	0.02	0.19	37	9792
Growth factor binding	MF	3.96	0.02	0.19	21	19838

Antigen processing and presentation of exogenous peptide antigen	BP	3.96	0.02	0.19	30	2478
Positive regulation of phagocytosis	BP	3.96	0.02	0.19	8	50766
Vesicle-mediated transport	BP	3.94	0.02	0.19	112	16192
Coated pit	CC	3.94	0.02	0.19	11	5905
Membrane organization	BP	3.94	0.02	0.19	64	61024
Glycosaminoglycan metabolic process	BP	3.94	0.02	0.19	27	30203
Divalent inorganic cation transmembrane transporter activity	MF	3.94	0.02	0.19	27	72509
Protein localization to membrane	BP	3.93	0.02	0.19	14	72657

Heart looping	BP	3.92	0.02	0.20	12	1947
Cell morphogenesis involved in differentiation	BP	3.92	0.02	0.20	22	904
Anchoring junction	CC	3.90	0.02	0.20	37	70161
Regulation of transcription involved in cell fate commitment	BP	3.89	0.02	0.20	5	60850
Spinal cord association neuron differentiation	BP	3.89	0.02	0.20	5	21527
Intrinsic to internal side of plasma membrane	CC	3.89	0.02	0.20	5	31235
Dorsal/ventral axis specification	BP	3.89	0.02	0.20	5	9950
Regulation of respiratory system process	BP	3.89	0.02	0.20	5	44065
Lens morphogenesis in	BP	3.89	0.02	0.20	5	2089

camera-type eye							
DNA-directed RNA	CC	3.89	0.02	0.20	5	5665	
polymerase II, core							
complex							
Actin monomer binding	MF	3.89	0.02	0.20	5	3785	
Central nervous system	BP	3.89	0.02	0.20	7	21954	
neuron development							
Mesenchymal cell	BP	3.89	0.02	0.20	7	14031	
development							
Positive regulation of	BP	3.89	0.02	0.20	7	45687	
glial cell differentiation							
Zinc ion binding	MF	3.88	0.02	0.20	280	8270	
Positive regulation of	BP	3.86	0.02	0.20	9	45762	
adenylate cyclase							
activity							
Endosomal part	CC	3.86	0.02	0.20	53	44440	
Neurotransmitter:sodium	MF	3.85	0.02	0.20	6	5328	

symporter activity						
Regulation of	BP	3.85	0.02	0.20	6	2000677
transcription regulatory						
region DNA binding						
Cytoskeletal protein	MF	3.85	0.02	0.20	97	8092
binding						
Regulation of cellular	BP	3.84	0.02	0.20	458	31326
biosynthetic process						
Regulation of molecular	BP	3.84	0.02	0.21	254	65009
function						
Anion transmembrane	MF	3.83	0.02	0.21	40	8509
transporter activity						
Polysaccharide	BP	3.83	0.02	0.21	15	5976
metabolic process						
Regulation of stem cell	BP	3.83	0.02	0.21	15	2000736
differentiation						
Anatomical structure	BP	3.82	0.02	0.21	29	60249

homeostasis						
Regulation of	BP	3.81	0.02	0.21	10	32652
interleukin-1 production						
Stem cell proliferation	BP	3.81	0.02	0.21	10	72089
Antigen processing and	BP	3.81	0.02	0.21	30	19884
presentation of						
exogenous antigen						
Myosin complex	CC	3.80	0.02	0.21	14	16459
Membrane part	CC	3.80	0.02	0.21	808	44425
Voltage-gated channel	MF	3.80	0.02	0.21	31	22832
activity						
Voltage-gated ion	MF	3.80	0.02	0.21	31	5244
channel activity						
Regulation of adenylate	BP	3.79	0.02	0.21	13	45761
cyclase activity						
Regulation of cartilage	BP	3.79	0.02	0.21	11	61035
development						

Positive regulation of lipase activity	BP	3.78	0.02	0.21	17	60193
Organelle membrane	CC	3.78	0.02	0.21	307	31090
Positive regulation of JNK cascade	BP	3.78	0.02	0.21	12	46330
Regulation of cell motility	BP	3.78	0.02	0.21	66	2000145
Synapse	CC	3.78	0.02	0.21	34	45202
Positive regulation of cytoskeleton organization	BP	3.77	0.02	0.21	21	51495
Regulation of neuron projection development	BP	3.77	0.02	0.21	36	10975
Cell part morphogenesis	BP	3.77	0.02	0.21	38	32990
Cell differentiation in spinal cord	BP	3.76	0.02	0.21	8	21515
Face morphogenesis	BP	3.76	0.02	0.21	8	60325

Stem cell development	BP	3.76	0.02	0.21	8	48864
Activation of adenylate cyclase activity	BP	3.76	0.02	0.21	8	7190
Embryo development	BP	3.74	0.02	0.21	52	9790
Heterocyclic compound binding	MF	3.72	0.02	0.22	709	1901363
Regulation of macromolecule metabolic process	BP	3.72	0.02	0.22	565	60255
Stress-activated MAPK cascade	BP	3.72	0.02	0.22	18	51403
Regulation of RNA metabolic process	BP	3.71	0.02	0.22	406	51252
Hexose metabolic process	BP	3.71	0.02	0.22	33	19318
Cell projection organization	BP	3.70	0.02	0.22	75	30030

Positive regulation of chemokine biosynthetic process	BP	3.70	0.02	0.22	4	45080
Hematopoietic stem cell proliferation	BP	3.70	0.02	0.22	4	71425
Regulation of development, heterochronic	BP	3.70	0.02	0.22	4	40034
Apical protein localization	BP	3.70	0.02	0.22	4	45176
Ventricular trabecula myocardium morphogenesis	BP	3.70	0.02	0.22	4	3222
Positive regulation of protein sumoylation	BP	3.70	0.02	0.22	4	33235
Pre-mrna binding	MF	3.70	0.02	0.22	4	36002
Peripheral nervous	BP	3.70	0.02	0.22	4	48935

system neuron						
development						
Metaphase	BP	3.70	0.02	0.22	4	51323
Regulation of	BP	3.70	0.02	0.22	4	32928
superoxide anion						
generation						
Activation of	BP	3.70	0.02	0.22	4	7171
transmembrane receptor						
protein tyrosine kinase						
activity						
DNA synthesis involved	BP	3.70	0.02	0.22	4	731
in DNA repair						
Positive regulation of	BP	3.70	0.02	0.22	4	60391
SMAD protein import						
into nucleus						
Basal transcription	MF	3.70	0.02	0.22	4	1098
machinery binding						

Basal RNA polymerase II transcription machinery binding	MF	3.70	0.02	0.22	4	1099
Protein domain specific binding	MF	3.69	0.03	0.22	79	19904
Cellular response to endogenous stimulus	BP	3.69	0.03	0.22	100	71495
Heterotrimeric G-protein complex	CC	3.69	0.03	0.22	9	5834
Regulation of lyase activity	BP	3.68	0.03	0.22	14	51339
Amino acid transmembrane transporter activity	MF	3.68	0.03	0.22	14	15171
Voltage-gated cation channel activity	MF	3.68	0.03	0.22	24	22843
Axon part	CC	3.68	0.03	0.22	24	33267

Positive regulation of protein catabolic process	BP	3.68	0.03	0.22	17	45732
Endoderm development	BP	3.67	0.03	0.22	7	7492
Chondroitin sulfate biosynthetic process	BP	3.67	0.03	0.22	7	30206
Dorsal/ventral pattern formation	BP	3.66	0.03	0.22	13	9953
Positive regulation of cell projection organization	BP	3.65	0.03	0.22	25	31346
Recycling endosome	CC	3.64	0.03	0.22	12	55037
Response to organic substance	BP	3.64	0.03	0.22	261	10033
Voltage-gated potassium channel activity	MF	3.63	0.03	0.22	16	5249

Regulation of biosynthetic process	BP	3.63	0.03	0.22	460	9889
Regulation of chemotaxis	BP	3.63	0.03	0.22	20	50920
Response to acid	BP	3.62	0.03	0.22	18	1101
Wnt receptor signaling pathway, calcium modulating pathway	BP	3.62	0.03	0.22	3	7223
Adenylate cyclase binding	MF	3.62	0.03	0.22	3	8179
Regulation of bile acid biosynthetic process	BP	3.62	0.03	0.22	3	70857
Neutrophil degranulation	BP	3.62	0.03	0.22	3	43312
Coumarin metabolic process	BP	3.62	0.03	0.22	3	9804
N-methyl-D-aspartate selective glutamate	MF	3.62	0.03	0.22	3	4972

receptor activity						
FACIT collagen	CC	3.62	0.03	0.22	3	5593
WINAC complex	CC	3.62	0.03	0.22	3	71778
COPI-coated vesicle	CC	3.62	0.03	0.22	3	30137
Eukaryotic initiation	MF	3.62	0.03	0.22	3	8190
factor 4E binding						
Opioid receptor	BP	3.62	0.03	0.22	3	38003
signaling pathway						
Nerve growth factor	MF	3.62	0.03	0.22	3	48406
binding						
Somatic muscle	BP	3.62	0.03	0.22	3	7525
development						
Positive regulation of	BP	3.62	0.03	0.22	3	2000052
non-canonical Wnt						
receptor signaling						
pathway						
Positive regulation of	BP	3.62	0.03	0.22	3	10890

sequestering of triglyceride							
Coronary vasculature	BP	3.62	0.03	0.22	3	60977	
morphogenesis							
Forebrain	BP	3.62	0.03	0.22	3	21797	
anterior/posterior pattern specification							
Glycine transmembrane transporter activity	MF	3.62	0.03	0.22	3	15187	
Laminin-1 binding	MF	3.62	0.03	0.22	3	43237	
Growth plate cartilage development	BP	3.62	0.03	0.22	3	3417	
Gene silencing by mirna	BP	3.62	0.03	0.22	3	35195	
Retina vasculature	BP	3.62	0.03	0.22	3	61299	
morphogenesis in camera-type eye							
Immunoglobulin	BP	3.62	0.03	0.22	3	2377	

production

JUN kinase binding	MF	3.62	0.03	0.22	3	8432
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Mitotic metaphase	BP	3.62	0.03	0.22	3	89
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Sensory perception of	BP	3.62	0.03	0.22	3	50916
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sweet taste

Chloride channel	MF	3.62	0.03	0.22	3	17081
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regulator activity

Collagen biosynthetic	BP	3.62	0.03	0.22	3	32964
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process

Endothelial cell	BP	3.60	0.03	0.22	6	45446
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differentiation

Activation of Rho gtpase	BP	3.60	0.03	0.22	6	32862
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activity

Intracellular ligand-	MF	3.60	0.03	0.22	6	5217
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gated ion channel

activity

Microfilament motor	MF	3.60	0.03	0.22	6	146
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activity						
Positive regulation of endocytosis	BP	3.59	0.03	0.22	15	45807
Carbohydrate homeostasis	BP	3.59	0.03	0.22	21	33500
Glucose homeostasis	BP	3.59	0.03	0.22	21	42593
Response to arsenic-containing substance	BP	3.59	0.03	0.22	5	46685
Alpha-mannosidase activity	MF	3.59	0.03	0.22	5	4559
Nua4 histone acetyltransferase complex	CC	3.59	0.03	0.22	5	35267
Axonemal dynein complex	CC	3.59	0.03	0.22	5	5858
Tubulin-tyrosine ligase activity	MF	3.59	0.03	0.22	5	4835

Extracellular region part	CC	3.58	0.03	0.22	160	44421
Negative regulation of cell growth	BP	3.57	0.03	0.22	25	30308
Regulation of lipid biosynthetic process	BP	3.57	0.03	0.22	19	46890
Tissue remodeling	BP	3.56	0.03	0.23	14	48771
Regulation of cell morphogenesis	BP	3.56	0.03	0.23	49	22604
Intracellular membrane-bounded organelle	CC	3.54	0.03	0.23	990	43231
Potassium ion transmembrane transporter activity	MF	3.53	0.03	0.23	23	15079
Metalloendopeptidase activity	MF	3.53	0.03	0.23	20	4222
Negative regulation of cell projection	BP	3.53	0.03	0.23	16	31345

organization

Regulation of exocytosis	BP	3.53	0.03	0.23	16	17157
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Endocytic vesicle	CC	3.53	0.03	0.23	16	30139
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Stress-activated protein	BP	3.52	0.03	0.23	18	31098
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kinase signaling

cascade

Adenyl ribonucleotide	MF	3.52	0.03	0.23	212	32559
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binding

Cellular response to	BP	3.52	0.03	0.23	9	71230
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amino acid stimulus

In utero embryonic	BP	3.51	0.03	0.23	35	1701
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development

Phosphotransferase	MF	3.51	0.03	0.23	107	16773
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activity, alcohol group

as acceptor

Intracellular organelle	CC	3.51	0.03	0.23	80	70013
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lumen

Neurotrophin TRK receptor signaling pathway	BP	3.51	0.03	0.23	44	48011
Embryonic organ development	BP	3.50	0.03	0.23	21	48568
Regulation of lipase activity	BP	3.50	0.03	0.23	21	60191
Skin development	BP	3.50	0.03	0.23	10	43588
Amide biosynthetic process	BP	3.50	0.03	0.23	11	43604
Protein kinase activity	MF	3.48	0.03	0.24	91	4672
Regulation of cell-cell adhesion	BP	3.48	0.03	0.24	15	22407
Epithelial cell differentiation	BP	3.48	0.03	0.24	41	30855
Embryonic limb morphogenesis	BP	3.47	0.03	0.24	17	30326

Embryonic appendage morphogenesis	BP	3.47	0.03	0.24	17	35113
ATP binding	MF	3.47	0.03	0.24	208	5524
Negative regulation of intracellular steroid hormone receptor signaling pathway	BP	3.46	0.03	0.24	7	33144
Vesicle docking involved in exocytosis	BP	3.46	0.03	0.24	7	6904
Glutamate receptor activity	MF	3.46	0.03	0.24	7	8066
Ephrin receptor signaling pathway	BP	3.46	0.03	0.24	7	48013
Negative regulation of stress-activated MAPK cascade	BP	3.46	0.03	0.24	7	32873
Negative regulation of	BP	3.46	0.03	0.24	7	70303

stress-activated protein						
kinase signaling						
cascade						
Neurotrophin signaling	BP	3.45	0.03	0.24	44	38179
pathway						
Transporter activity	MF	3.43	0.03	0.24	170	5215
Monosaccharide	BP	3.42	0.03	0.25	16	46365
catabolic process						
Notch signaling pathway	BP	3.41	0.03	0.25	21	7219
Positive regulation of	BP	3.41	0.03	0.25	13	32874
stress-activated MAPK						
cascade						
Positive regulation of	BP	3.41	0.03	0.25	13	10811
cell-substrate adhesion						
Organelle localization	BP	3.41	0.03	0.25	13	51640
Lysosomal membrane	CC	3.41	0.03	0.25	26	5765
Adenyl nucleotide	MF	3.40	0.03	0.25	212	30554

binding						
Proteinaceous	CC	3.39	0.03	0.25	36	5578
extracellular matrix						
Calcium ion	MF	3.39	0.03	0.25	22	15085
transmembrane						
transporter activity						
Chordate embryonic	BP	3.39	0.03	0.25	35	43009
development						
Endoplasmic reticulum	CC	3.39	0.03	0.25	29	5788
lumen						
Regulation of Ras	BP	3.39	0.03	0.25	29	32318
gtpase activity						
Antigen processing and	BP	3.38	0.03	0.25	31	48002
presentation of peptide						
antigen						
Response to amino acid	BP	3.37	0.03	0.25	15	43200
stimulus						

Positive regulation of phospholipase activity	BP	3.37	0.03	0.25	15	10518
Transition metal ion binding	MF	3.37	0.03	0.25	308	46914
Negative regulation of response to external stimulus	BP	3.37	0.03	0.25	23	32102
Regulation of gene expression	BP	3.37	0.03	0.25	455	10468
Regulation of embryonic development	BP	3.37	0.03	0.25	17	45995
Macromolecule metabolic process	BP	3.37	0.03	0.25	834	43170
Cellular macromolecule biosynthetic process	BP	3.37	0.03	0.25	355	34645
Polysaccharide catabolic process	BP	3.37	0.03	0.25	6	272

Adipose tissue development	BP	3.37	0.03	0.25	6	60612
Cardiac cell development	BP	3.37	0.03	0.25	6	55006
Homeostasis of number of cells within a tissue	BP	3.37	0.03	0.25	6	48873
Negative regulation of protein kinase B signaling cascade	BP	3.37	0.03	0.25	6	51898
Regulation of interleukin-4 production	BP	3.37	0.03	0.25	6	32673
Regulation of RNA biosynthetic process	BP	3.36	0.03	0.25	395	2001141
Negative regulation of muscle cell differentiation	BP	3.36	0.03	0.25	9	51148
Negative regulation of	BP	3.36	0.03	0.25	9	1901185

ERBB signaling pathway						
Negative regulation of epidermal growth factor receptor signaling pathway	BP	3.36	0.03	0.25	9	42059
Positive regulation of proteasomal protein catabolic process	BP	3.36	0.03	0.25	9	1901800
Integral to plasma membrane	CC	3.35	0.04	0.25	145	5887
MHC protein complex	CC	3.35	0.04	0.25	10	42611
RNA polymerase activity	MF	3.35	0.04	0.25	10	34062
DNA-directed RNA polymerase activity	MF	3.35	0.04	0.25	10	3899
Regulation of organ morphogenesis	BP	3.34	0.04	0.25	25	2000027

Glandular epithelial cell development	BP	3.34	0.04	0.25	4	2068
Negative chemotaxis	BP	3.34	0.04	0.25	4	50919
Intramolecular transferase activity, phosphotransferases	MF	3.34	0.04	0.25	4	16868
Positive regulation of translational initiation	BP	3.34	0.04	0.25	4	45948
Platelet alpha granule	CC	3.34	0.04	0.25	4	31091
Heart trabecula morphogenesis	BP	3.34	0.04	0.25	4	61384
Myelin maintenance	BP	3.34	0.04	0.25	4	43217
Regulation of Wnt receptor signaling pathway, planar cell polarity pathway	BP	3.34	0.04	0.25	4	2000095
Regulation of antigen	BP	3.34	0.04	0.25	4	2577

processing and presentation						
Dipeptidyl-peptidase activity	MF	3.34	0.04	0.25	4	8239
Positive regulation of steroid biosynthetic process	BP	3.34	0.04	0.25	4	10893
RNA polymerase core enzyme binding	MF	3.34	0.04	0.25	4	43175
Phosphorylation	BP	3.34	0.04	0.25	96	16310
Positive regulation of organ growth	BP	3.32	0.04	0.25	5	46622
Translation initiation factor binding	MF	3.32	0.04	0.25	5	31369
Nitric oxide mediated signal transduction	BP	3.32	0.04	0.25	5	7263
Organ formation	BP	3.32	0.04	0.25	5	48645

Vitamin D receptor binding	MF	3.32	0.04	0.25	5	42809
H4/H2A histone acetyltransferase complex	CC	3.32	0.04	0.25	5	43189
Negative regulation of toll-like receptor signaling pathway	BP	3.32	0.04	0.25	5	34122
Nucleotide-sugar biosynthetic process	BP	3.32	0.04	0.25	5	9226
Regulation of cellular macromolecule biosynthetic process	BP	3.31	0.04	0.25	426	2000112
Calcium ion binding	MF	3.29	0.04	0.25	99	5509
Positive regulation of stress-activated protein kinase signaling	BP	3.29	0.04	0.25	13	70304

cascade						
Positive regulation of phospholipase C activity	BP	3.29	0.04	0.25	13	10863
Metabolic process						
Monosaccharide	BP	3.27	0.04	0.25	36	5996
Basement membrane						
Basement membrane	CC	3.27	0.04	0.25	15	5604
Hexose catabolic process						
Hexose catabolic process	BP	3.27	0.04	0.25	15	19320
Positive regulation of neural precursor cell proliferation						
Positive regulation of neural precursor cell proliferation	BP	3.27	0.04	0.25	7	2000179
Substrate adhesion-dependent cell spreading						
Substrate adhesion-dependent cell spreading	BP	3.27	0.04	0.25	7	34446
Calcium-dependent cell-cell adhesion						
Calcium-dependent cell-cell adhesion	BP	3.27	0.04	0.25	7	16339
Enhancer sequence-						
Enhancer sequence-	MF	3.27	0.04	0.25	7	1158

specific DNA binding							
Regulated secretory pathway	BP	3.27	0.04	0.25	7	45055	
Autophagic vacuole	CC	3.27	0.04	0.25	7	5776	
Positive regulation of stem cell proliferation	BP	3.26	0.04	0.25	12	2000648	
Activation of phospholipase C activity	BP	3.26	0.04	0.25	12	7202	
Chondroitin sulfate metabolic process	BP	3.26	0.04	0.25	12	30204	
Calmodulin binding	MF	3.25	0.04	0.25	28	5516	
Positive regulation of interleukin-6 production	BP	3.22	0.04	0.25	8	32755	
Regulation of actin filament depolymerization	BP	3.22	0.04	0.25	8	30834	
Negative regulation of	BP	3.22	0.04	0.25	8	10812	

cell-substrate adhesion						
Cell projection	BP	3.21	0.04	0.25	35	48858
morphogenesis						
Actin cytoskeleton	BP	3.20	0.04	0.25	9	31532
reorganization						
Extracellular matrix	MF	3.20	0.04	0.25	9	50840
binding						
Ammonium	BP	3.20	0.04	0.25	2	72488
transmembrane						
transport						
Prostaglandin-E	MF	3.20	0.04	0.25	2	50220
synthase activity						
Trehalose metabolic	BP	3.20	0.04	0.25	2	5991
process						
Seminiferous tubule	BP	3.20	0.04	0.25	2	72520
development						
Cardiac atrium	BP	3.20	0.04	0.25	2	3209

morphogenesis						
Regulation of collateral sprouting in absence of injury	BP	3.20	0.04	0.25	2	48696
Spemann organizer formation	BP	3.20	0.04	0.25	2	60061
Regulation of exocyst localization	BP	3.20	0.04	0.25	2	60178
Dehydroascorbic acid transporter activity	MF	3.20	0.04	0.25	2	33300
D-glucose transmembrane transporter activity	MF	3.20	0.04	0.25	2	55056
Production of mirnas involved in gene silencing by mirna	BP	3.20	0.04	0.25	2	35196
Melatonin receptor	MF	3.20	0.04	0.25	2	8502

activity						
Hypothalamus cell	BP	3.20	0.04	0.25	2	21979
differentiation						
Collagen type IX	CC	3.20	0.04	0.25	2	5594
Negative regulation of	BP	3.20	0.04	0.25	2	10621
transcription by						
transcription factor						
localization						
Detection of	BP	3.20	0.04	0.25	2	9726
endogenous stimulus						
Autonomic nervous	BP	3.20	0.04	0.25	2	48483
system development						
Trophectodermal	BP	3.20	0.04	0.25	2	1831
cellular morphogenesis						
Sec61 translocon	CC	3.20	0.04	0.25	2	5784
complex						
Translocon complex	CC	3.20	0.04	0.25	2	71256

Brain segmentation	BP	3.20	0.04	0.25	2	35284
Cell migration involved in endocardial cushion formation	BP	3.20	0.04	0.25	2	3273
Transcription initiation from RNA polymerase III promoter	BP	3.20	0.04	0.25	2	6384
Calcium ion-dependent exocytosis of neurotransmitter	BP	3.20	0.04	0.25	2	48791
Dendritic growth cone	CC	3.20	0.04	0.25	2	44294
Natriuretic peptide receptor activity	MF	3.20	0.04	0.25	2	16941
Metencephalon development	BP	3.20	0.04	0.25	2	22037
Diencephalon morphogenesis	BP	3.20	0.04	0.25	2	48852

Cardiac vascular smooth muscle cell development	BP	3.20	0.04	0.25	2	60948
Vasoactive intestinal polypeptide receptor activity	MF	3.20	0.04	0.25	2	4999
Transcription initiation from mitochondrial promoter	BP	3.20	0.04	0.25	2	6391
G-quadruplex DNA binding	MF	3.20	0.04	0.25	2	51880
Butyrate metabolic process	BP	3.20	0.04	0.25	2	19605
Chromosome movement towards spindle pole	BP	3.20	0.04	0.25	2	51305
Phenylpropanoid catabolic process	BP	3.20	0.04	0.25	2	46271

Cerebral cortex regionalization	BP	3.20	0.04	0.25	2	21796
Regulation of defense response to bacterium	BP	3.20	0.04	0.25	2	1900424
Regulation of phagocytosis, engulfment	BP	3.20	0.04	0.25	2	60099
Positive regulation of phagocytosis, engulfment	BP	3.20	0.04	0.25	2	60100
Cellular pigmentation	BP	3.20	0.04	0.25	2	33059
Synaptic cleft	CC	3.20	0.04	0.25	2	43083
Regulation of nodal signaling pathway involved in determination of left/right asymmetry	BP	3.20	0.04	0.25	2	1900145

Regulation of nodal signaling pathway involved in determination of lateral mesoderm left/right asymmetry	BP	3.20	0.04	0.25	2	1900175
Establishment or maintenance of neuroblast polarity	BP	3.20	0.04	0.25	2	45196
Establishment of neuroblast polarity	BP	3.20	0.04	0.25	2	45200
Sensory system development	BP	3.20	0.04	0.25	2	48880
Cardiac muscle cell myoblast differentiation	BP	3.20	0.04	0.25	2	60379
Collagen V binding	MF	3.20	0.04	0.25	2	70052
Forebrain neuron fate	BP	3.20	0.04	0.25	2	21877

commitment						
Regulation of transcription from RNA polymerase II promoter involved in spinal cord motor neuron fate specification	BP	3.20	0.04	0.25	2	21912
Neural plate pattern specification	BP	3.20	0.04	0.25	2	60896
Neural plate regionalization	BP	3.20	0.04	0.25	2	60897
Synaptic vesicle clustering	BP	3.20	0.04	0.25	2	97091
Bombesin receptor activity	MF	3.20	0.04	0.25	2	4946
Locomotion involved in locomotory behavior	BP	3.20	0.04	0.25	2	31987

Regulation of transcription from RNA polymerase II promoter involved in determination of left/right symmetry	BP	3.20	0.04	0.25	2	1900094
Nodal signaling pathway involved in determination of lateral mesoderm left/right asymmetry	BP	3.20	0.04	0.25	2	1900164
Nodal signaling pathway involved in determination of left/right asymmetry	BP	3.20	0.04	0.25	2	38107
Smooth muscle cell proliferation	BP	3.20	0.04	0.25	2	48659

Pre-mrna intronic binding	MF	3.20	0.04	0.25	2	97157
Intestinal epithelial cell development	BP	3.20	0.04	0.25	2	60576
Negative regulation of cholesterol biosynthetic process	BP	3.20	0.04	0.25	2	45541
Negative regulation of cholesterol metabolic process	BP	3.20	0.04	0.25	2	90206
Actin polymerization- dependent cell motility	BP	3.20	0.04	0.25	2	70358
Protein poly-ADP- ribosylation	BP	3.20	0.04	0.25	2	70212
Viral assembly, maturation, egress, and release	BP	3.20	0.04	0.25	2	19067

Retinal blood vessel	BP	3.20	0.04	0.25	2	61304
morphogenesis						
Ornithine decarboxylase	MF	3.20	0.04	0.25	2	42978
activator activity						
Intestine smooth muscle	BP	3.20	0.04	0.25	2	14827
contraction						
Calcium-dependent	MF	3.20	0.04	0.25	2	4698
protein kinase C activity						
Calcium-dependent	MF	3.20	0.04	0.25	2	9931
protein serine/threonine						
kinase activity						
Laminin-11 complex	CC	3.20	0.04	0.25	2	43260
Positive regulation of	BP	3.19	0.04	0.25	69	51345
hydrolase activity						
Regulation of MAPK	BP	3.19	0.04	0.25	71	43408
cascade						
Ubiquitin protein ligase	MF	3.19	0.04	0.25	26	31625

binding						
Small conjugating	MF	3.19	0.04	0.25	26	44389
protein ligase binding						
Transcription initiation	BP	3.19	0.04	0.25	31	6367
from RNA polymerase II						
promoter						
Regulation of purine	BP	3.18	0.04	0.25	20	1900371
nucleotide biosynthetic						
process						
Regulation of nucleotide	BP	3.18	0.04	0.25	20	30808
biosynthetic process						
Transcriptional	CC	3.18	0.04	0.25	13	17053
repressor complex						
Ion transport	BP	3.17	0.04	0.25	130	6811
Regulation of	BP	3.17	0.04	0.25	391	6355
transcription, DNA-						
dependent						

Positive regulation of purine nucleotide metabolic process	BP	3.17	0.04	0.25	15	1900544
Negative regulation of binding	BP	3.17	0.04	0.25	15	51100
Wnt receptor signaling pathway, planar cell polarity pathway	BP	3.16	0.04	0.25	6	60071
Regulation of establishment of planar polarity	BP	3.16	0.04	0.25	6	90175
Negative regulation of glial cell differentiation	BP	3.16	0.04	0.25	6	45686
Motor neuron axon guidance	BP	3.16	0.04	0.25	6	8045
Laminin binding	MF	3.16	0.04	0.25	6	43236
Regulation of cytokine	BP	3.15	0.04	0.25	3	2739

secretion involved in							
immune response							
Galactose catabolic	BP	3.15	0.04	0.25	3	19388	
process							
Filtration diaphragm	CC	3.15	0.04	0.25	3	36056	
Slit diaphragm	CC	3.15	0.04	0.25	3	36057	
Relaxation of smooth	BP	3.15	0.04	0.25	3	44557	
muscle							
Embryonic process	BP	3.15	0.04	0.25	3	60136	
involved in female							
pregnancy							
Regulation of neuron	BP	3.15	0.04	0.25	3	2001222	
migration							
Cellular extravasation	BP	3.15	0.04	0.25	3	45123	
Interkinetic nuclear	BP	3.15	0.04	0.25	3	22027	
migration							
CD4-positive or CD8-	BP	3.15	0.04	0.25	3	43369	

positive, alpha-beta T cell lineage commitment						
H3 histone acetyltransferase complex	CC	3.15	0.04	0.25	3	70775
MOZ/MORF histone acetyltransferase complex	CC	3.15	0.04	0.25	3	70776
Trna transcription	BP	3.15	0.04	0.25	3	9304
Neuronal cell body membrane	CC	3.15	0.04	0.25	3	32809
Cell body membrane	CC	3.15	0.04	0.25	3	44298
MAP-kinase scaffold activity	MF	3.15	0.04	0.25	3	5078
Positive regulation of dendritic cell antigen processing and	BP	3.15	0.04	0.25	3	2606

presentation

Nuclear envelope lumen	CC	3.15	0.04	0.25	3	5641
Laminin-1 complex	CC	3.15	0.04	0.25	3	5606
Cell cortex part	CC	3.15	0.04	0.25	18	44448
Enzyme activator	MF	3.15	0.04	0.25	64	8047

activity

Protein secretion	BP	3.14	0.04	0.26	12	9306
Regulation of cell	BP	3.13	0.04	0.26	61	30334

migration

Regulation of	BP	3.12	0.04	0.26	16	1505
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neurotransmitter levels

Visual perception	BP	3.12	0.04	0.26	30	7601
Dendrite	CC	3.12	0.04	0.26	30	30425
Detection of external	BP	3.12	0.04	0.26	26	9581

stimulus

Monocarboxylic acid	BP	3.12	0.04	0.26	28	72330
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biosynthetic process

Central nervous system development	BP	3.10	0.04	0.26	20	7417
Activating transcription factor binding	MF	3.10	0.04	0.26	11	33613
Negative regulation of cellular response to growth factor stimulus	BP	3.09	0.05	0.27	17	90288
G-protein coupled peptide receptor activity	MF	3.09	0.05	0.27	21	8528
E-box binding	MF	3.08	0.05	0.27	7	70888
Myeloid cell activation involved in immune response	BP	3.08	0.05	0.27	7	2275
Vesicle docking	BP	3.08	0.05	0.27	7	48278
Excretion	BP	3.07	0.05	0.27	10	7588
Negative regulation of steroid biosynthetic	BP	3.07	0.05	0.27	5	10894

process							
SMAD protein signal	BP	3.07	0.05	0.27	5	60395	
transduction							
External encapsulating	CC	3.07	0.05	0.27	5	44462	
structure part							
RNA polymerase II	MF	3.07	0.05	0.27	5	980	
distal enhancer							
sequence-specific DNA							
binding							
Mannosidase activity	MF	3.07	0.05	0.27	5	15923	
Positive regulation of	BP	3.07	0.05	0.27	5	2052	
neuroblast proliferation							
Protein phosphatase 2A	MF	3.07	0.05	0.27	5	51721	
binding							
Histone	MF	3.07	0.05	0.27	5	35035	
acetyltransferase							
binding							

Regulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate selective glutamate receptor activity	BP	3.07	0.05	0.27	5	2000311
Protein targeting to plasma membrane	BP	3.07	0.05	0.27	5	72661
Muscle cell proliferation	BP	3.07	0.05	0.27	5	33002
Positive regulation of nucleotide metabolic process	BP	3.07	0.05	0.27	15	45981
Cellular polysaccharide metabolic process	BP	3.07	0.05	0.27	13	44264
Potassium ion transport	BP	3.06	0.05	0.27	18	6813
Lateral plasma membrane	CC	3.06	0.05	0.27	8	16328

Defense response to Gram-positive bacterium	BP	3.06	0.05	0.27	8	50830
Positive regulation of exocytosis	BP	3.06	0.05	0.27	8	45921
Receptor regulator activity	MF	3.06	0.05	0.27	9	30545
Cardiocyte differentiation	BP	3.06	0.05	0.27	9	35051
Forelimb morphogenesis	BP	3.06	0.05	0.27	9	35136
Positive regulation of axonogenesis	BP	3.06	0.05	0.27	9	50772
Phagocytosis	BP	3.06	0.05	0.27	9	6909
Cell-cell adhesion	BP	3.06	0.05	0.27	54	16337
Transcription regulatory region sequence- specific DNA binding	MF	3.05	0.05	0.27	28	976

Regulation of macromolecule biosynthetic process	BP	3.05	0.05	0.27	434	10556
Chemical homeostasis	BP	3.04	0.05	0.27	107	48878
Oxidation-reduction process	BP	3.04	0.05	0.27	73	55114
Leydig cell differentiation	BP	3.04	0.05	0.27	4	33327
Trabecula morphogenesis	BP	3.04	0.05	0.27	4	61383
Positive regulation of interferon-gamma biosynthetic process	BP	3.04	0.05	0.27	4	45078
Positive regulation of insulin-like growth factor receptor signaling pathway	BP	3.04	0.05	0.27	4	43568

Mitogen-activated protein kinase kinase binding	MF	3.04	0.05	0.27	4	31434
Regulation of non- canonical Wnt receptor signaling pathway	BP	3.04	0.05	0.27	4	2000050
Chronic inflammatory response	BP	3.04	0.05	0.27	4	2544
Regulation of SMAD protein import into nucleus	BP	3.04	0.05	0.27	4	60390
Regulation of steroid hormone biosynthetic process	BP	3.04	0.05	0.27	4	90030
Histone H2A acetylation	BP	3.04	0.05	0.27	4	43968
Negative regulation of JUN kinase activity	BP	3.04	0.05	0.27	4	43508

Fibrillar collagen	CC	3.04	0.05	0.27	4	5583
Cellular response to chemical stimulus	BP	3.03	0.05	0.27	214	70887
Regulation of phospholipase activity	BP	3.03	0.05	0.27	16	10517
Positive regulation of locomotion	BP	3.02	0.05	0.27	39	40017
Fatty acid biosynthetic process	BP	3.02	0.05	0.27	20	6633
Telomere maintenance	BP	3.02	0.05	0.27	12	723
Steroid metabolic process	BP	3.01	0.05	0.27	38	8202
Golgi cisterna membrane	CC	3.01	0.05	0.27	14	32580
Peptide receptor activity	MF	3.01	0.05	0.27	21	1653
Epidermal growth factor receptor signaling	BP	3.00	0.05	0.27	31	7173

pathway						
Regulation of cytokine	BP	3.00	0.05	0.27	17	42035
biosynthetic process						
Positive regulation of	BP	3.00	0.05	0.27	30	43410
MAPK cascade						
Cellular chemical	BP	3.00	0.05	0.27	80	55082
homeostasis						
Nervous system	BP	2.99	0.05	0.27	44	7399
development						
Endopeptidase inhibitor	MF	2.99	0.05	0.28	28	4866
activity						
Endoplasmic reticulum-	CC	2.98	0.05	0.28	11	5793
Golgi intermediate						
compartment						
Extrinsic to internal side	CC	2.98	0.05	0.28	11	31234
of plasma membrane						
Regulation of striated	BP	2.97	0.05	0.28	15	51153

muscle cell						
differentiation						
Regulation of interferon-	BP	2.96	0.05	0.28	13	32649
gamma production						
Positive regulation of	BP	2.96	0.05	0.28	6	32731
interleukin-1 beta						
production						
Calcium activated cation	MF	2.96	0.05	0.28	6	5227
channel activity						
Regulation of	BP	2.96	0.05	0.28	6	48713
oligodendrocyte						
differentiation						
Neural tube	BP	2.96	0.05	0.28	6	21915
development						
Phosphatidylinositol 3-	MF	2.96	0.05	0.28	6	43548
kinase binding						
Middle ear	BP	2.96	0.05	0.28	6	42474

morphogenesis						
Positive regulation of cellular component biogenesis	BP	2.96	0.05	0.28	6	44089
Cellular homeostasis	BP	2.95	0.05	0.28	91	19725
ERBB signaling pathway	BP	2.94	0.05	0.28	31	38127
Cellular macromolecule localization	BP	2.94	0.05	0.29	36	70727
Regulation of ERK1 and ERK2 cascade	BP	2.93	0.05	0.29	21	70372
Regulation of hydrolase activity	BP	2.93	0.05	0.29	110	51336
Regulation of intracellular protein kinase cascade	BP	2.93	0.05	0.29	101	10627
Protein binding, bridging	MF	2.93	0.05	0.29	22	30674

Response to oxygen- containing compound	BP	2.92	0.05	0.29	135	1901700
Ventricular cardiac muscle tissue morphogenesis	BP	2.92	0.05	0.29	9	55010
Neuron-neuron synaptic transmission	BP	2.92	0.05	0.29	9	7270
Hindlimb morphogenesis	BP	2.92	0.05	0.29	9	35137
Regulation of cellular response to growth factor stimulus	BP	2.92	0.05	0.29	26	90287
Homophilic cell adhesion	BP	2.92	0.05	0.29	24	7156
Cellular response to organic substance	BP	2.92	0.05	0.29	184	71310
Protein tyrosine kinase	MF	2.92	0.05	0.29	25	4713

activity						
Locomotor behavior	BP	2.92	0.05	0.29	25	7626
Receptor activator	MF	2.91	0.05	0.29	7	30546
activity						
Negative regulation of gliogenesis	BP	2.91	0.05	0.29	7	14014
Golgi-associated vesicle	CC	2.91	0.05	0.29	7	5798
Positive regulation of proteolysis	BP	2.91	0.05	0.29	14	45862
Extracellular ligand-gated ion channel activity	MF	2.91	0.05	0.29	14	5230
Telomere organization	BP	2.91	0.05	0.29	12	32200
Negative regulation of BMP signaling pathway	BP	2.91	0.05	0.29	8	30514
Frizzled binding	MF	2.91	0.05	0.29	8	5109
Delayed rectifier	MF	2.91	0.05	0.29	8	5251

potassium channel

activity

627 BP, Biological process; MF, molecular function; cellular component; #, number of; GO ID, gene ontology identification.

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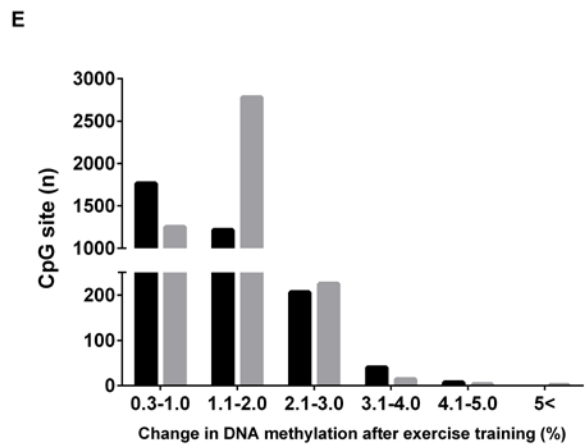
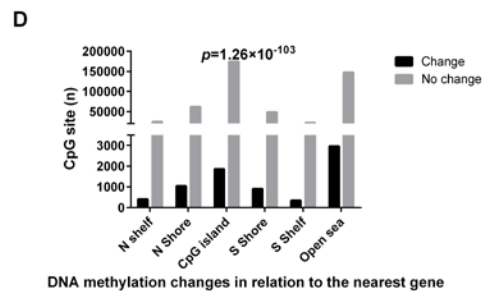
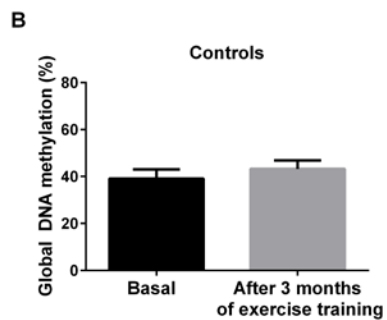
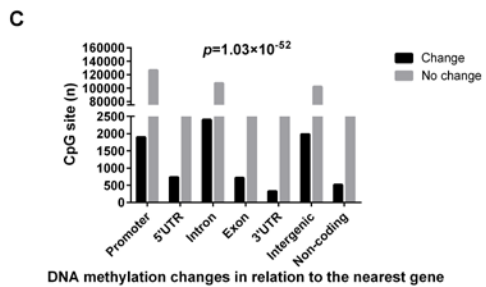
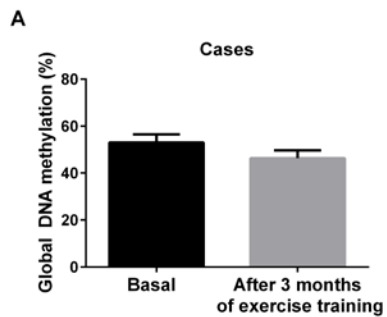
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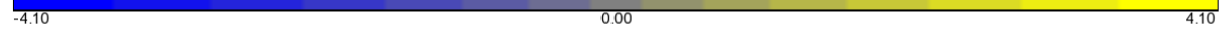
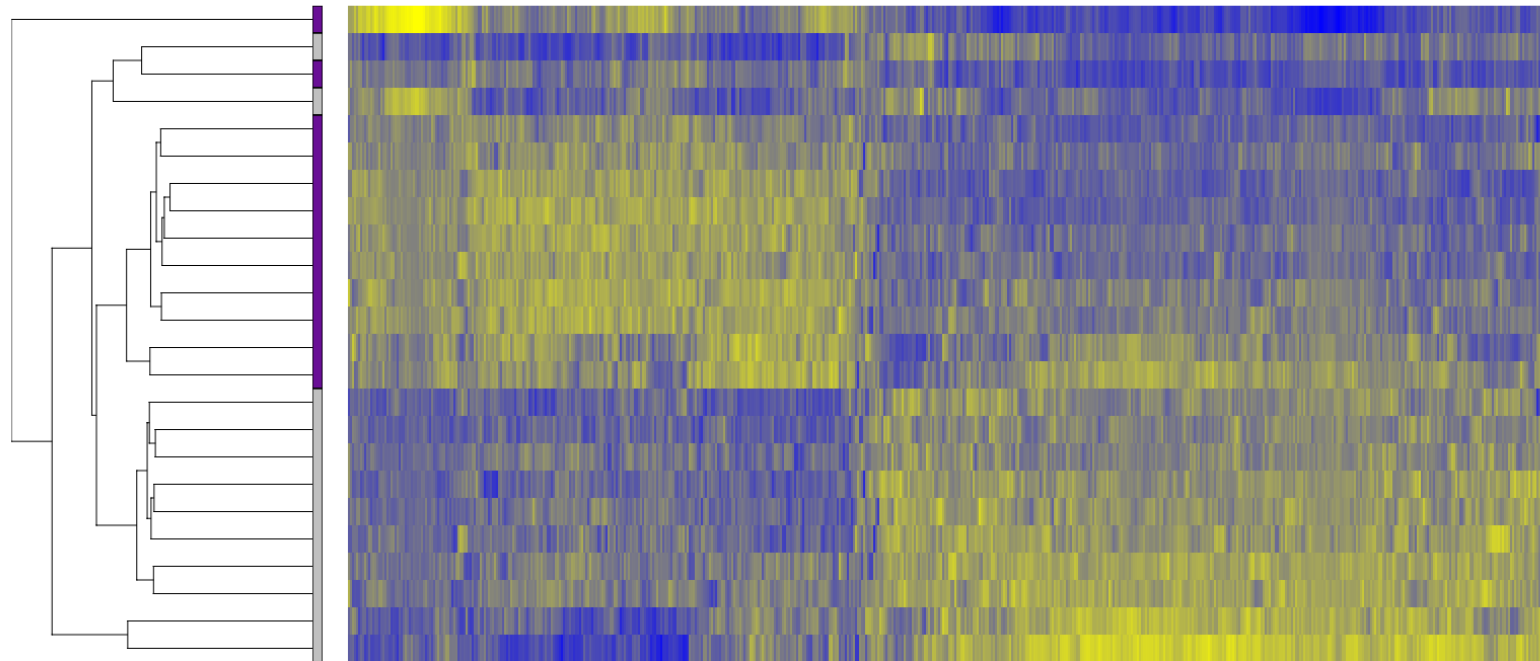
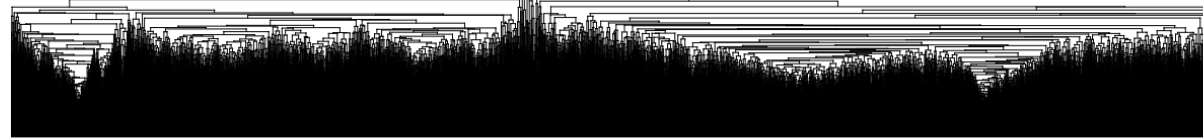
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Hierarchical Clustering of CpG sites differentially methylated after 3 months of exercise training

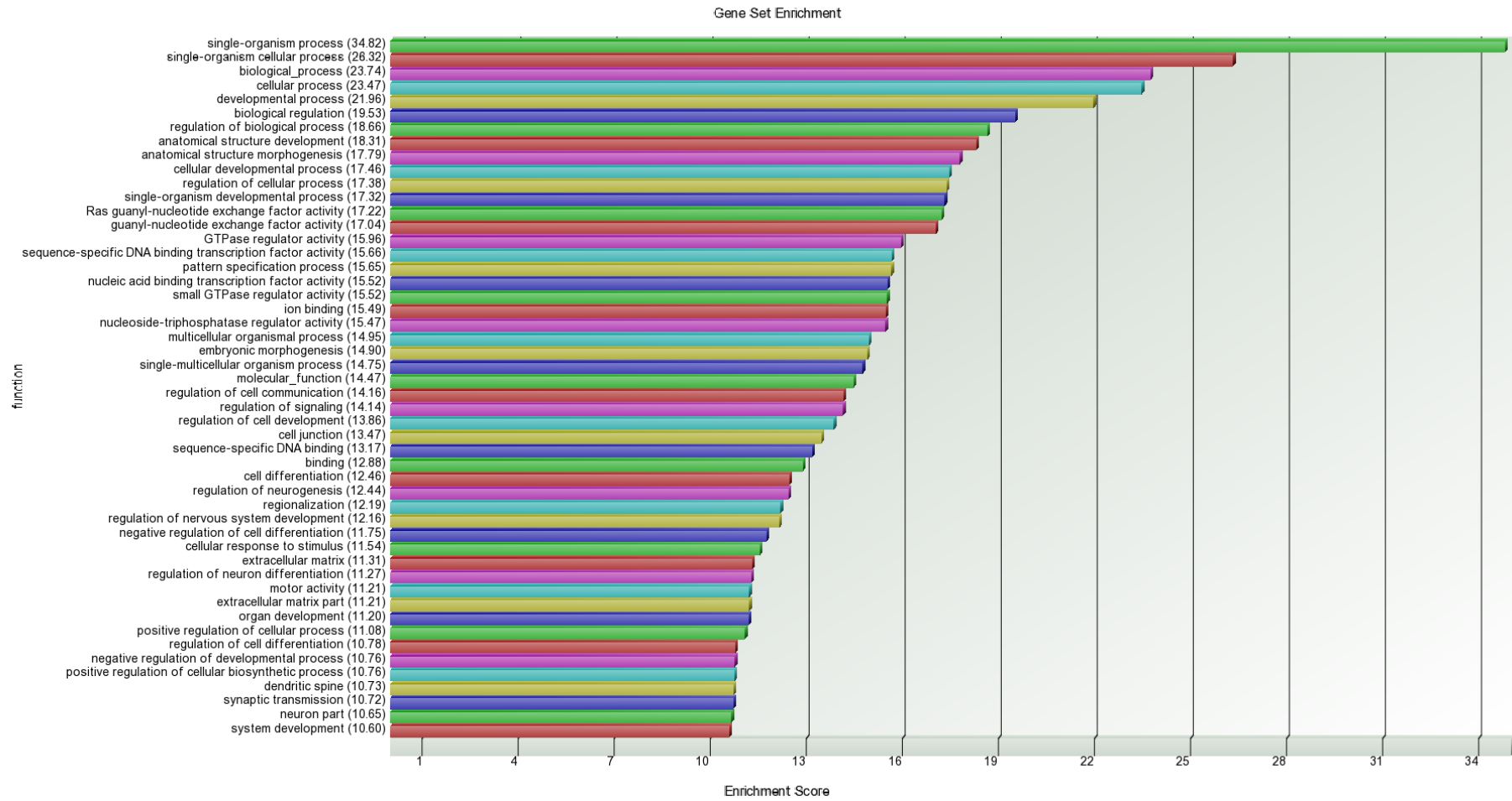


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Disease annotation analysis

