Supplemental Data File 8:

Genes Regulated by Caloric Restriction Have Unique Roles within Transcriptional Networks

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This file provides analyses of 16 genes for which mutations have been found to increase mouse lifespan (Prop1, Pit1, Ghr, Ghrhr, Irs2, PappA, Shc1, Igf1r, Kl, Adcy5, Surf1, Insr, Clk1, Ucp2, Irs1, Gpx4). Section I examines the local connectivity properties of these 16 genes (pgs 2−6), while section II examines non−local connectivity properties of the 16 genes (pgs 7−11). The variability among genes in terms of local connectivity is analyzed in section III (pgs 12−13). Section IV characterizes the expression module in which each of the 16 genes is embedded by identifying neighbors of each gene within the genome−wide transcriptional network (pgs 14−25).

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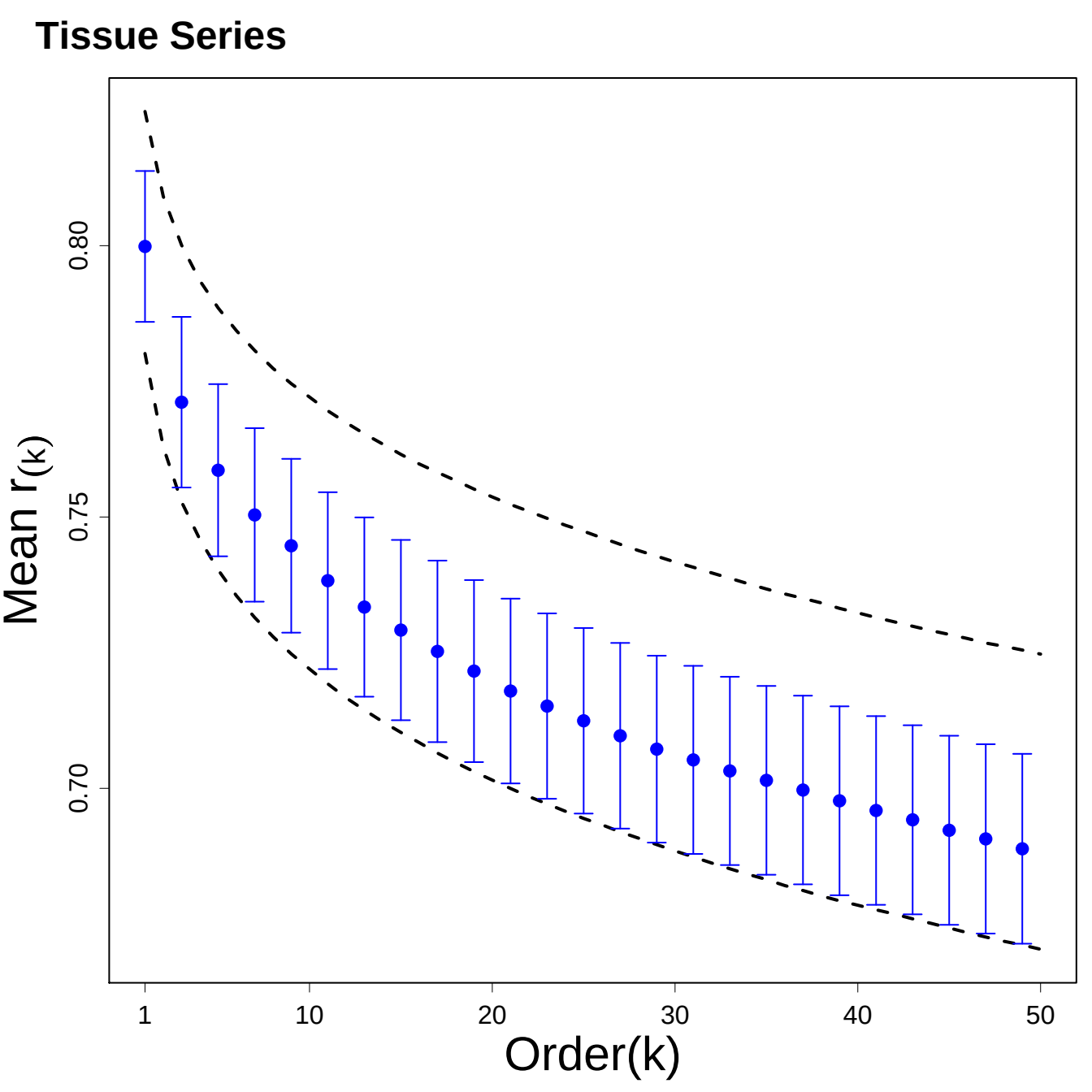
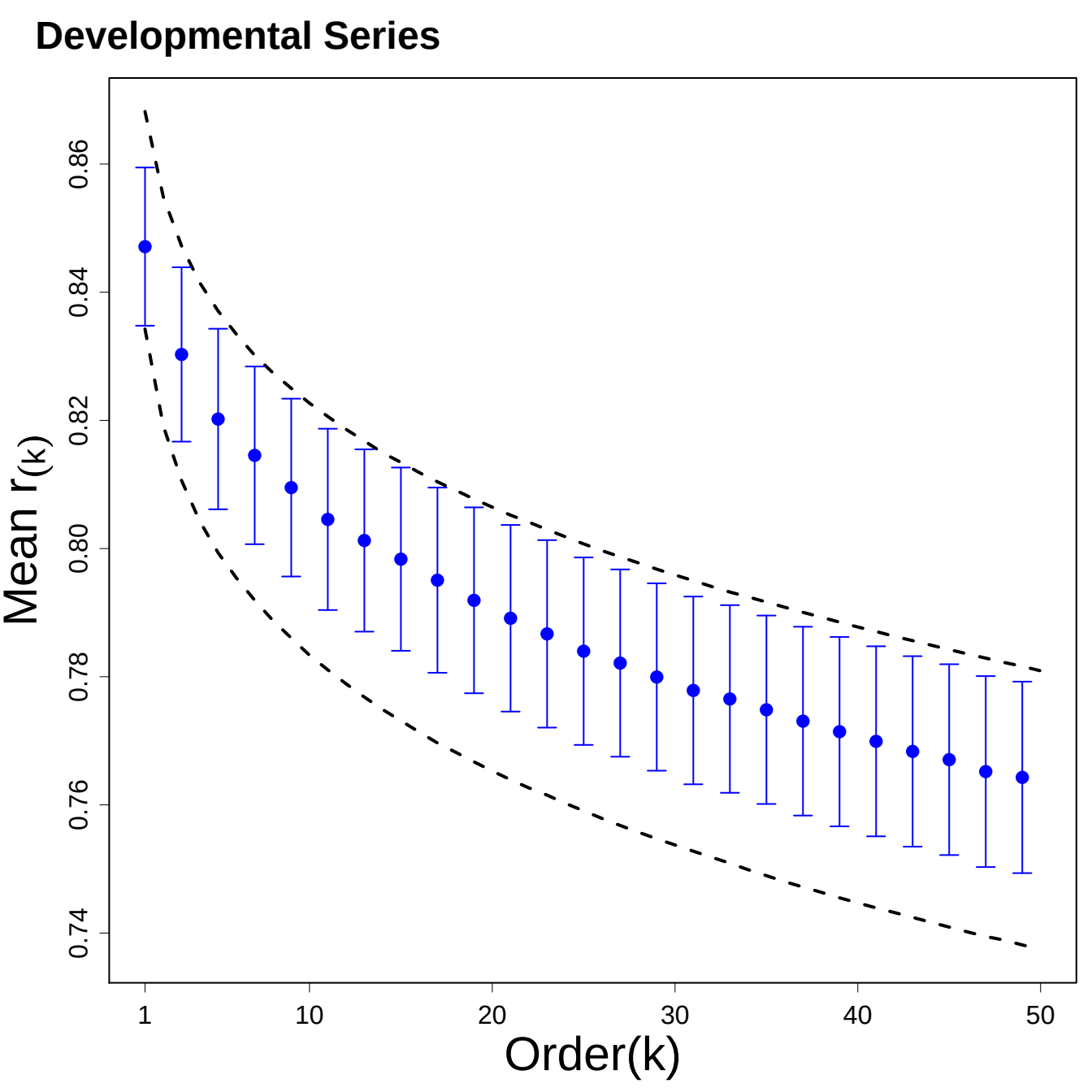
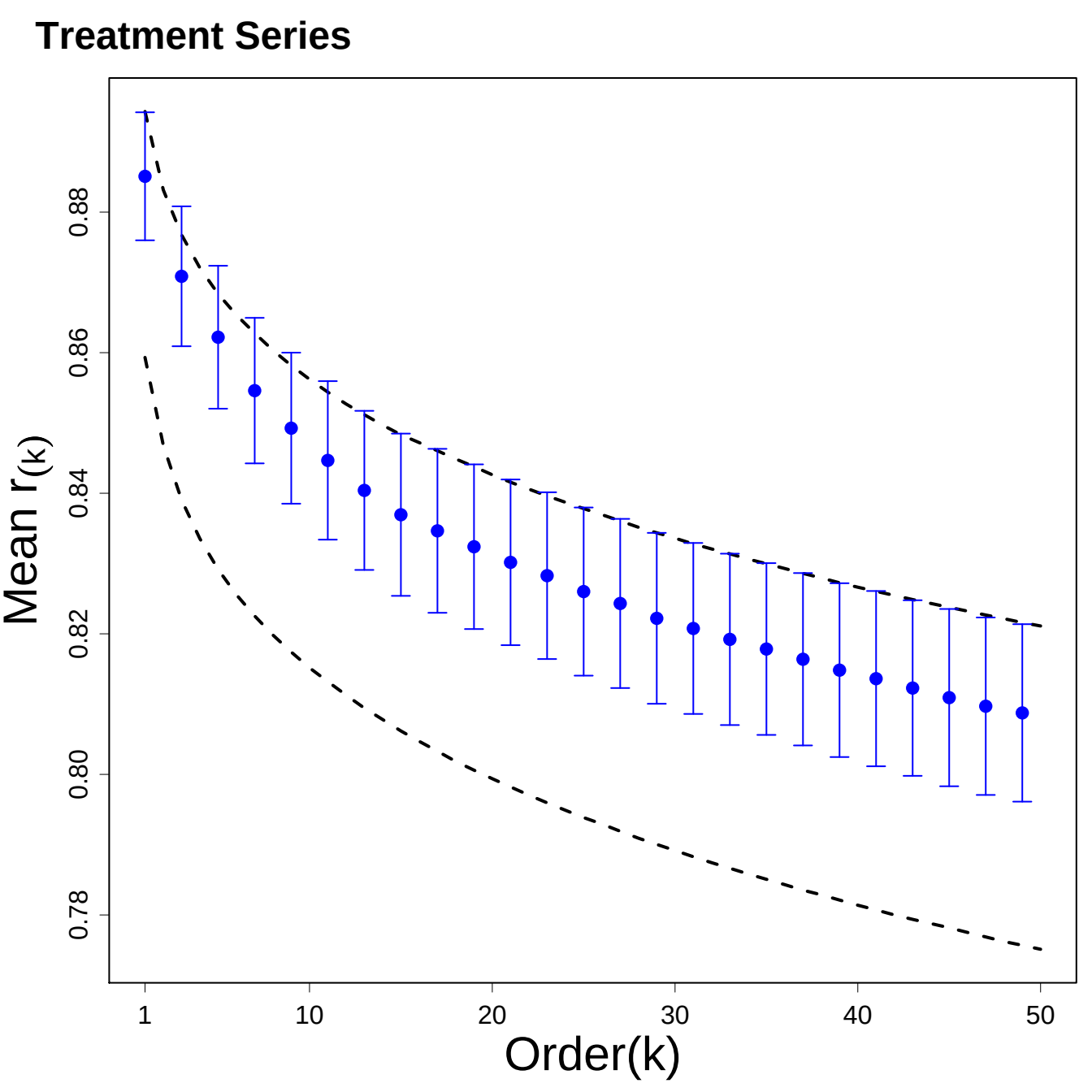
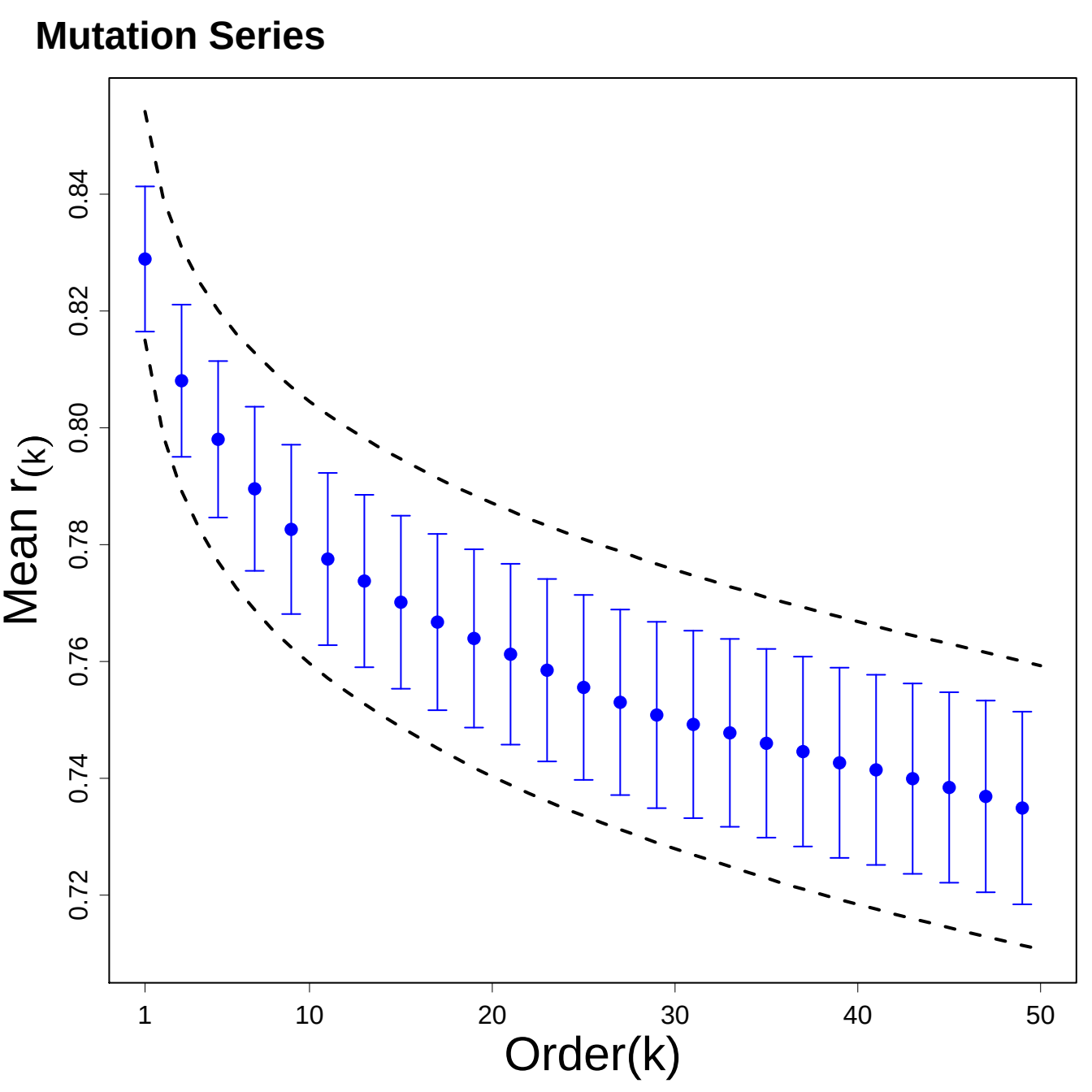
Section I: Local Connectivity

The next pages provide analyses of the local connectivity properties of the 16 genes for which mutations influence mouse lifespan (compare with Figure 4). The analysis is based on n = 31 transcripts that correspond to these 16 genes of interest, but similar results are obtained using only one transcript per gene of interest. Four graphics are shown, corresponding to the Tissue, Developmental, Treatment, and Mutation series, respectively. In each image, the vertical axis represents the average kth correlation order statistic (among n transcripts) and the horizontal axis corresponds to k. For a given transcript, the kth correlation order statistic equals the kth largest correlation between that transcript and all others represented on the Affymetrix Mouse 430 2.0 microarray. Highly connected transcripts should have a larger correlation order statistic for a given value of k. Blue points represent the average kth correlation order statistic among the n = 31 transcripts associated with the 16 genes of interest. Dashed black lines outline a 95% confidence region for the average kth correlation order statistic among n transcripts sampled at random (based upon simulation). In 95% of 10,000 simulation trials, random samples of n transcripts from the Affymetrix Mouse 430 2.0 array yielded an average kth correlation order statistic within the dashed lines.


Tissue Series
Mean r(k)
0.80
0.75
0.70
1
10
20
30
40
50
Order(k)

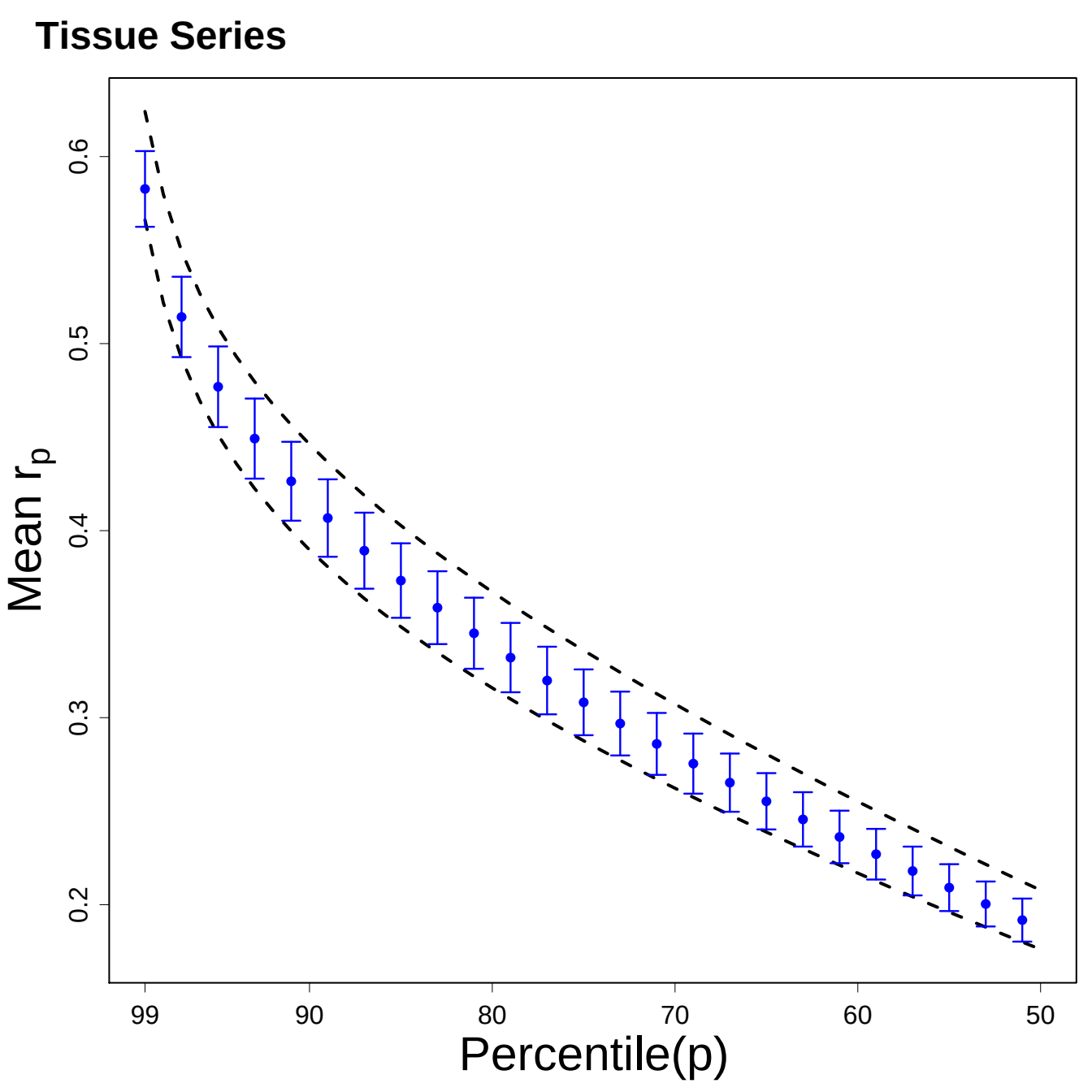

Developmental Series
Mean r(k)
0.74
0.76
0.78
0.80
0.82
0.84
0.86
1
10
20
30
40
50
Order(k)

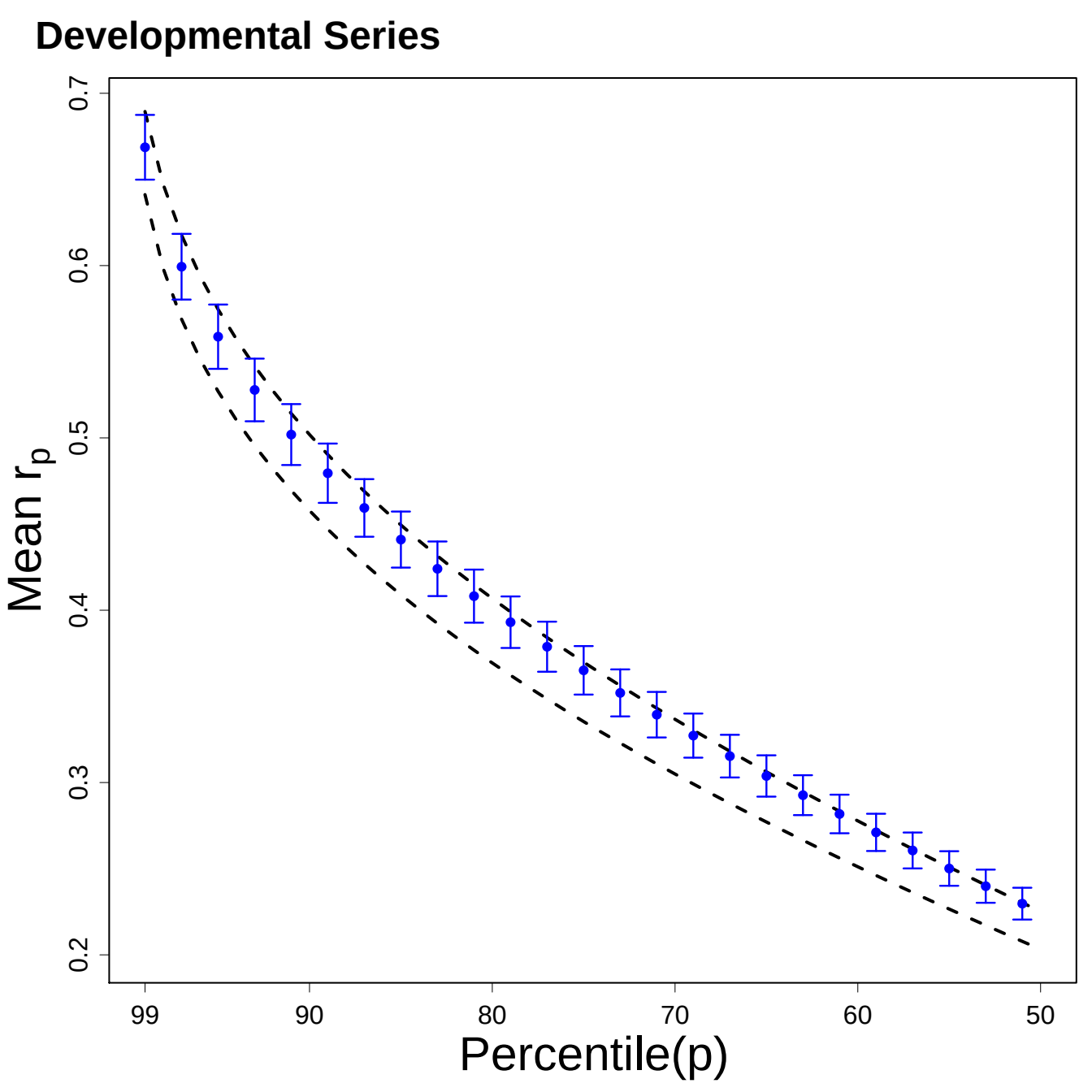

Treatment Series
Mean r(k)
0.78
0.80
0.82
0.84
0.86
0.88
1
10
20
30
40
50
Order(k)

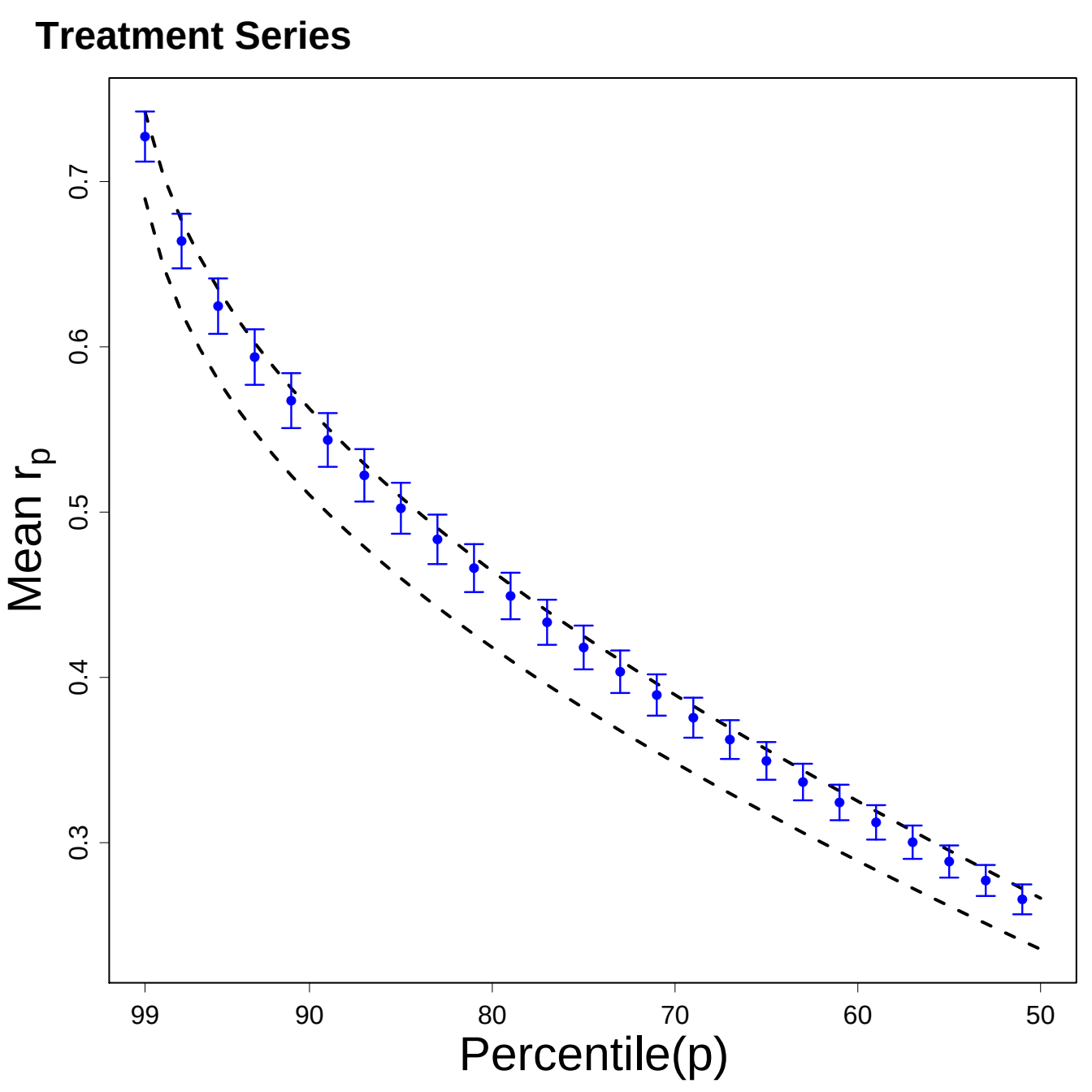

Mutation Series
Mean r(k)
0.72
0.74
0.76
0.78
0.80
0.82
0.84
1
10
20
30
40
50
Order(k)

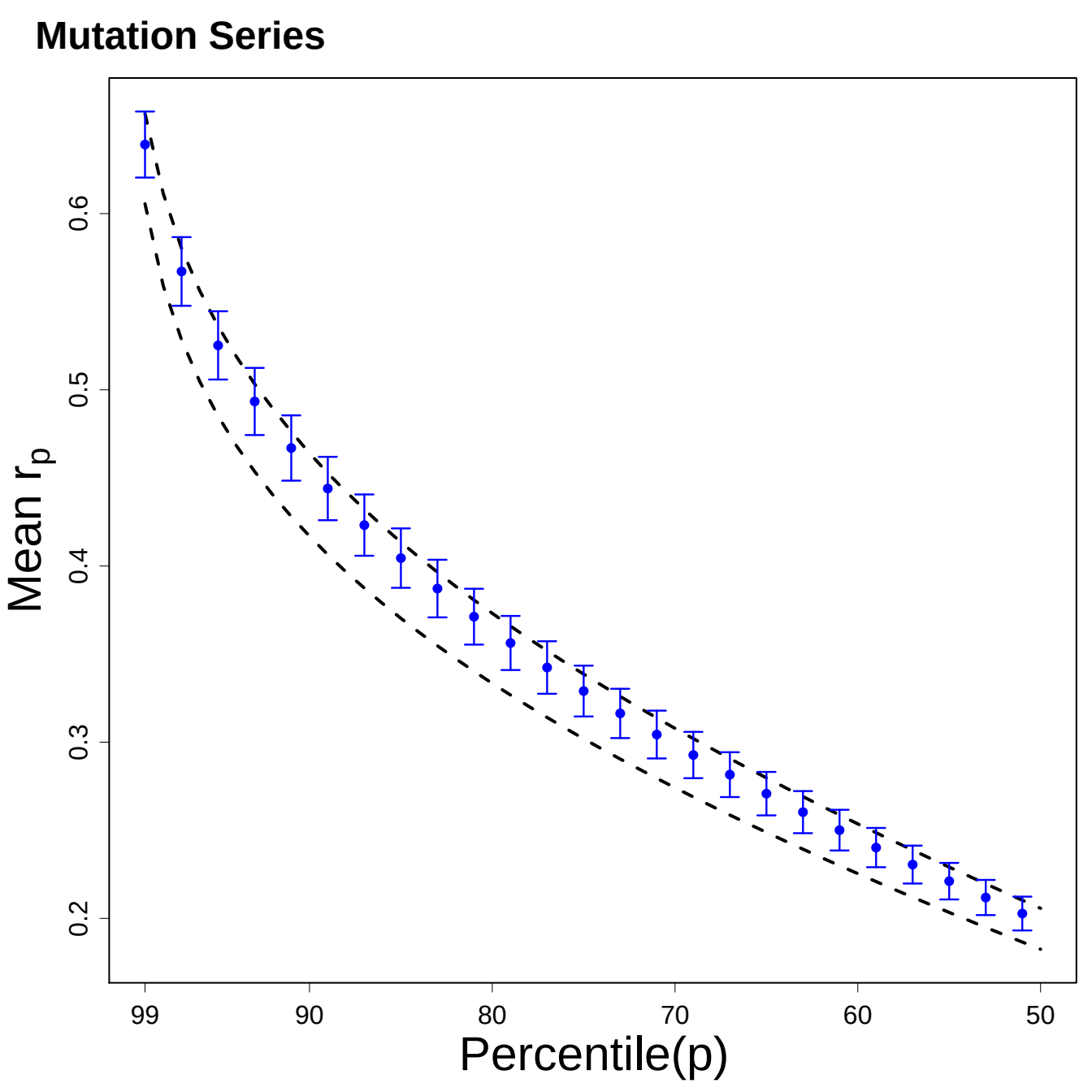
Section II: Non−local Connectivity

The next pages provide analyses of the non−local connectivity properties of the 16 genes for which mutations influence mouse lifespan (compare with Figure 7). The analysis is based on n = 31 transcripts that correspond to these 16 genes of interest, but similar results are obtained using only one transcript per gene of interest. Four graphics are shown, corresponding to the Tissue, Developmental, Treatment, and Mutation series, respectively. In each image, the vertical axis represents the average pth correlation percentile (among n transcripts) and the horizontal axis corresponds to p. For a given transcript, correlations with all other transcripts on the Affymetrix Mouse 430 2.0 array were determined, and the pth correlation percentile is the correlation value that is larger than p percent of all of these correlations. Transcripts that have strong “distant” connections should have large correlation percentiles. Blue points represent the average pth correlation percentile among the n = 31 transcripts associated with the 16 genes of interest. Dashed black lines outline a 95% confidence region for the average pth correlation percentile among n transcripts sampled at random (based upon simulation). In 95% of 10,000 simulation trials, random samples of n genes from the Affymetrix Mouse 430 2.0 array yielded an average pth correlation percentile within the dashed lines.


Tissue Series
Mean r_p
0.2
0.3
0.4
0.5
0.6
99
90
80
70
60
50
Percentile(p)

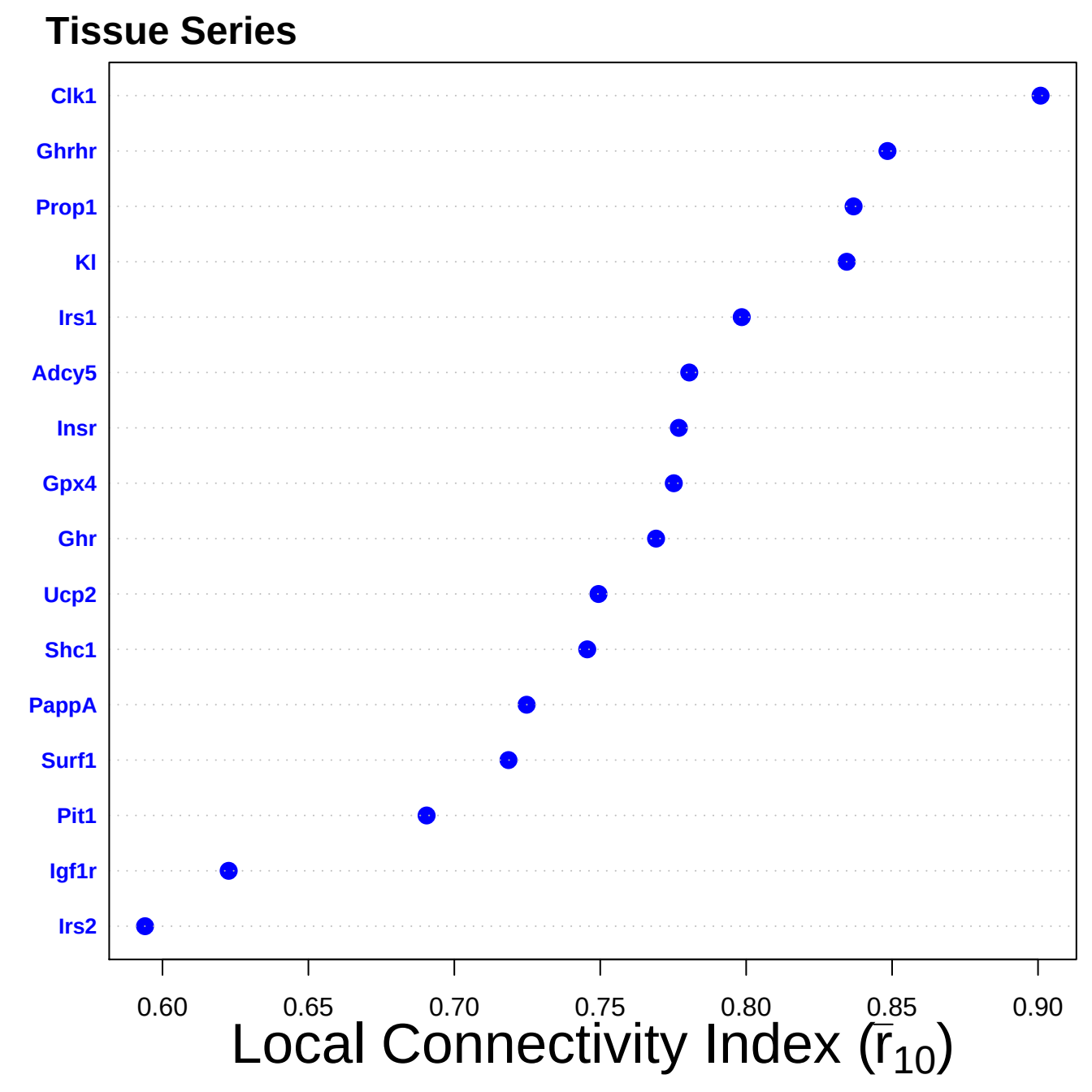

Developmental Series
Mean r_p
0.7
0.6
0.5
0.4
0.3
0.2
99
90
80
70
60
50
Percentile(p)

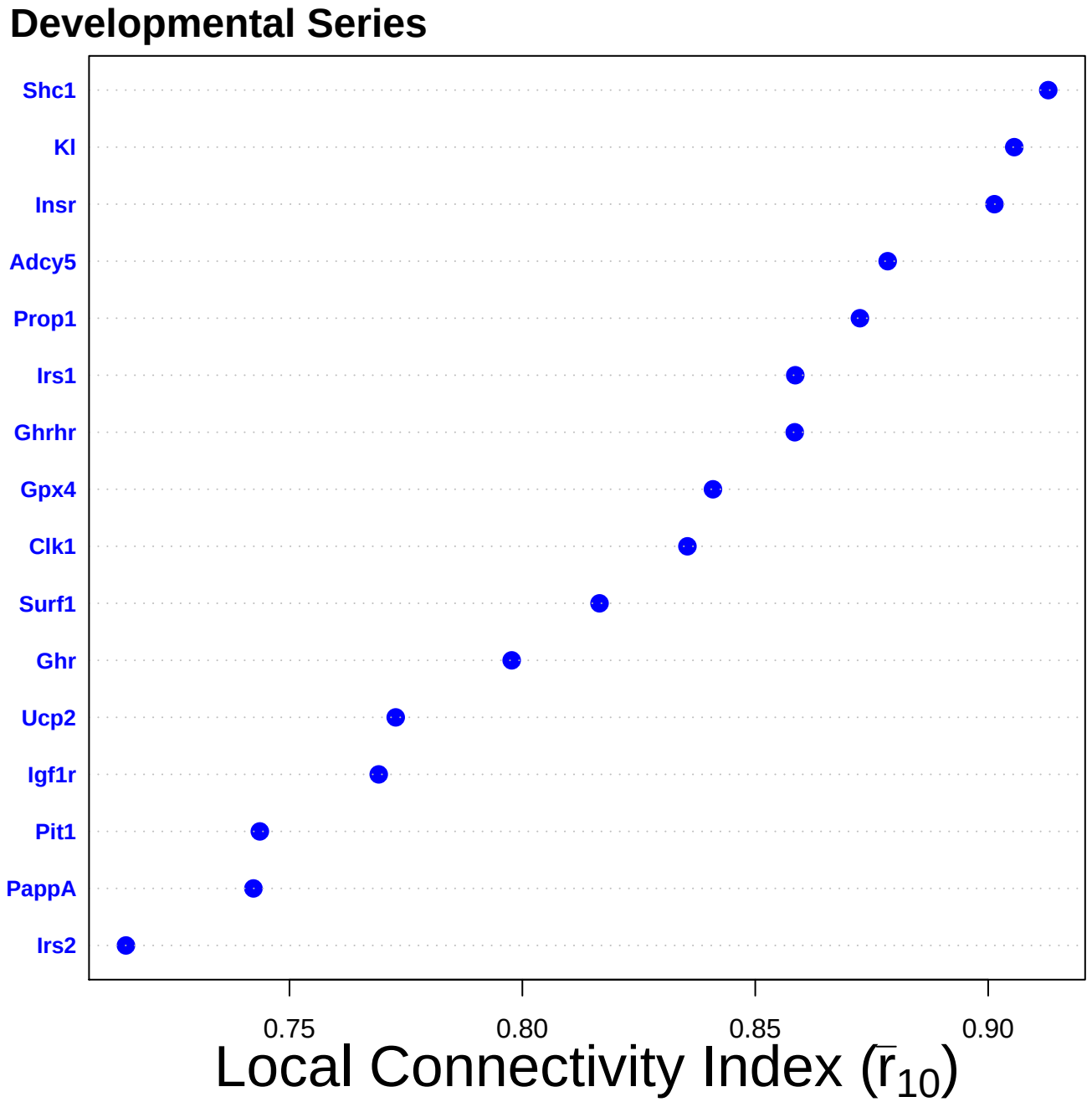

Treatment Series
Mean r_p
0.7
0.6
0.5
0.4
0.3
99
90
80
70
60
50
Percentile(p)

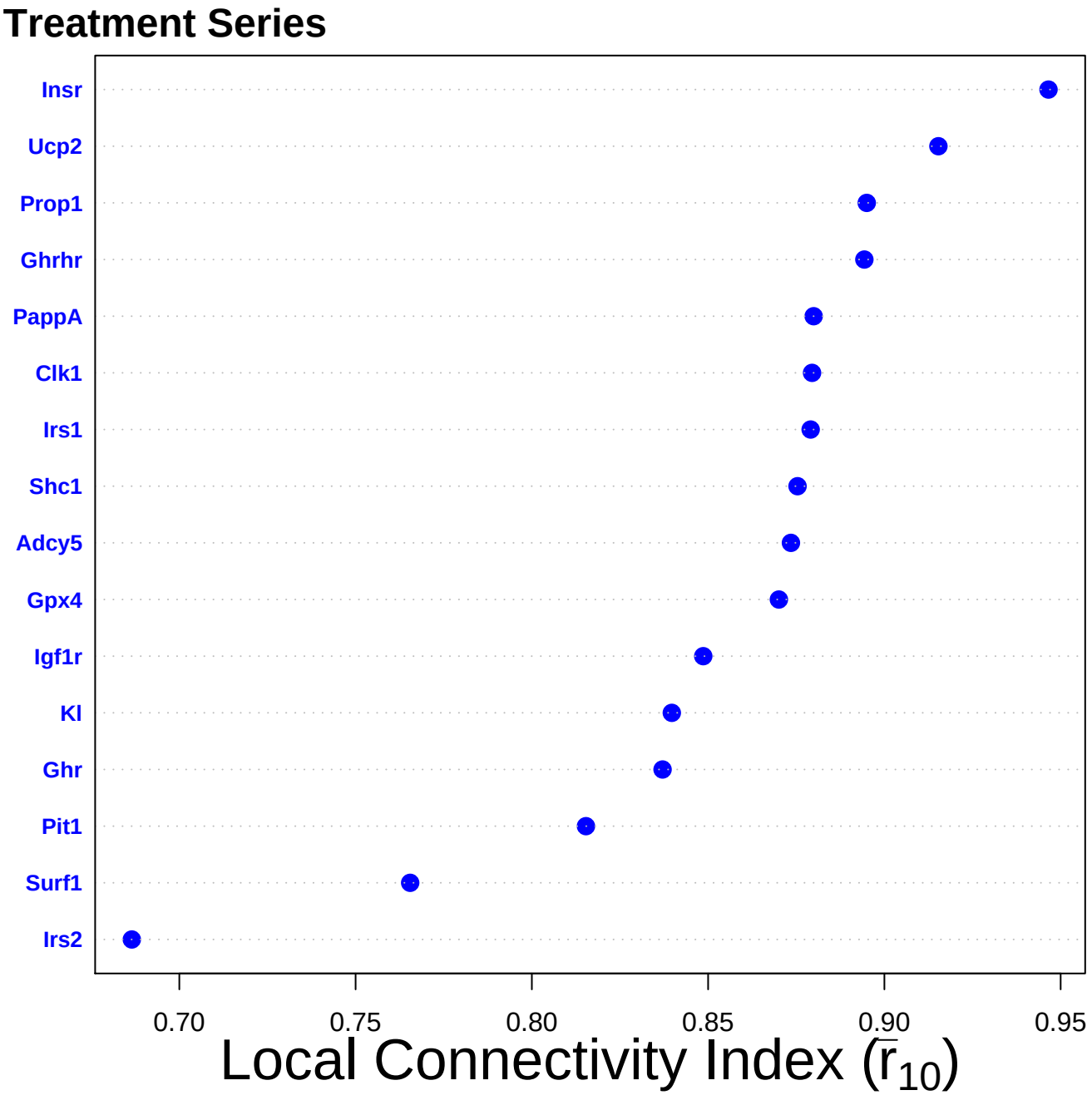

Mutation Series
Mean r_p
0.2
0.3
0.4
0.5
0.6
99
90
80
70
60
50
Percentile(p)

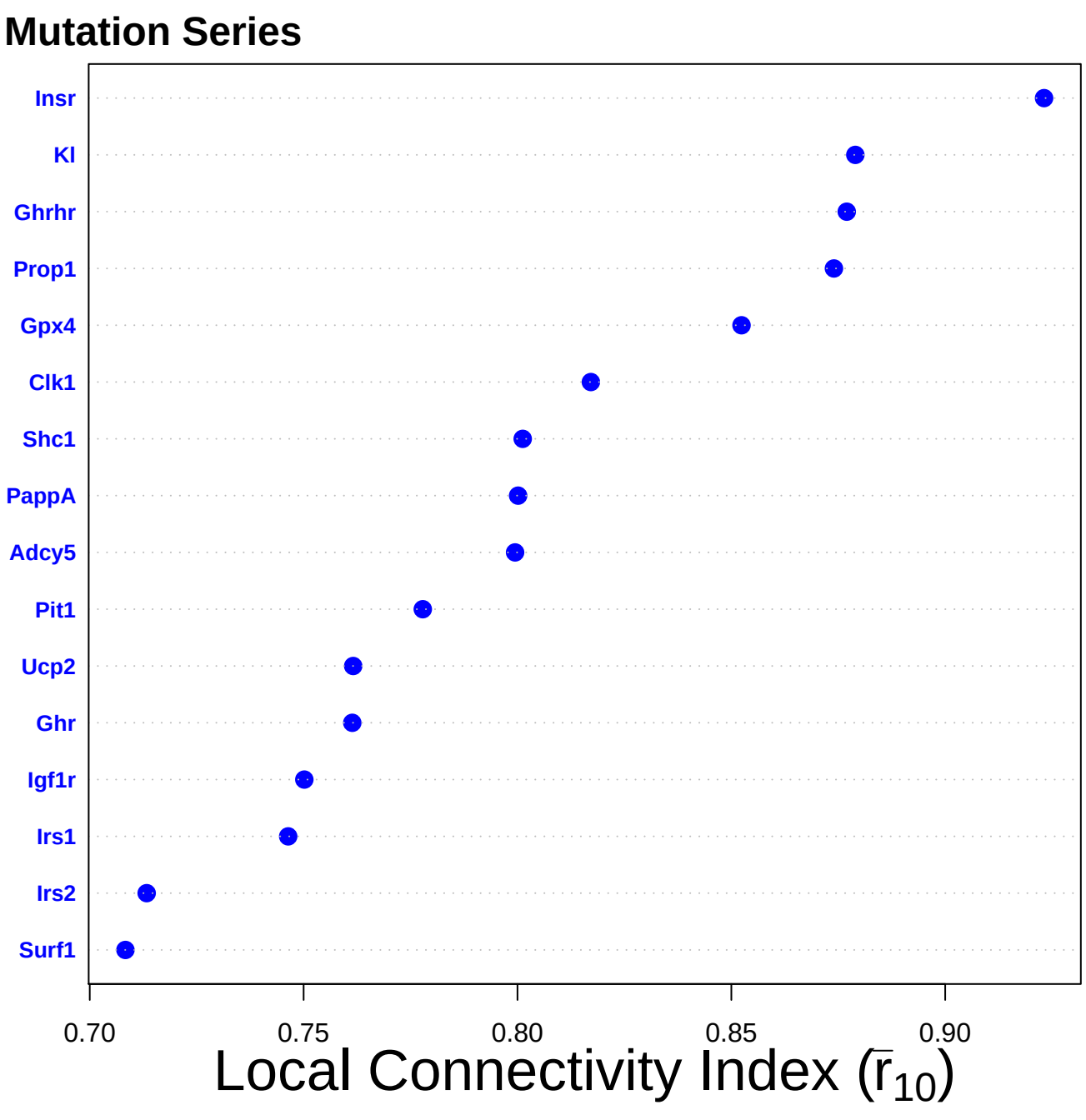
Section III: Local Connectivity Index

The next pages show plots of the local connectivity index for 16 lifespan−associated genes with respect to each of four independent datasets (Tissue, Developmental, Treatment and Mutation Series). The local connectivity index is directly related to the density of the local region immediately surrounding a given gene within the genome−wide transcriptional network. Based on this metric, each image lists the 16 genes of interest in the order of most to least connected, given the dataset indicated in the upper left hand corner of the figure. For some genes, more than one transcript was represented on the Affymetrix Mouse 430 2.0 array. In such cases, the local connectvity index was first calculated for each transcript individually and then averaged among transcripts corresponding to the same gene symbol.


Tissue Series
Clk1
Ghrhr
Prop1
Kl
Irs1
Adcy5
Insr
Gpx4
Ghr
Ucp2
Shc1
PappA
Surf1
Pit1
Igf1r
Irs2
0.60
0.65
0.70
0.75
0.80
0.85
0.90
Local Connectivity Index ($\bar{r}_{10}$)

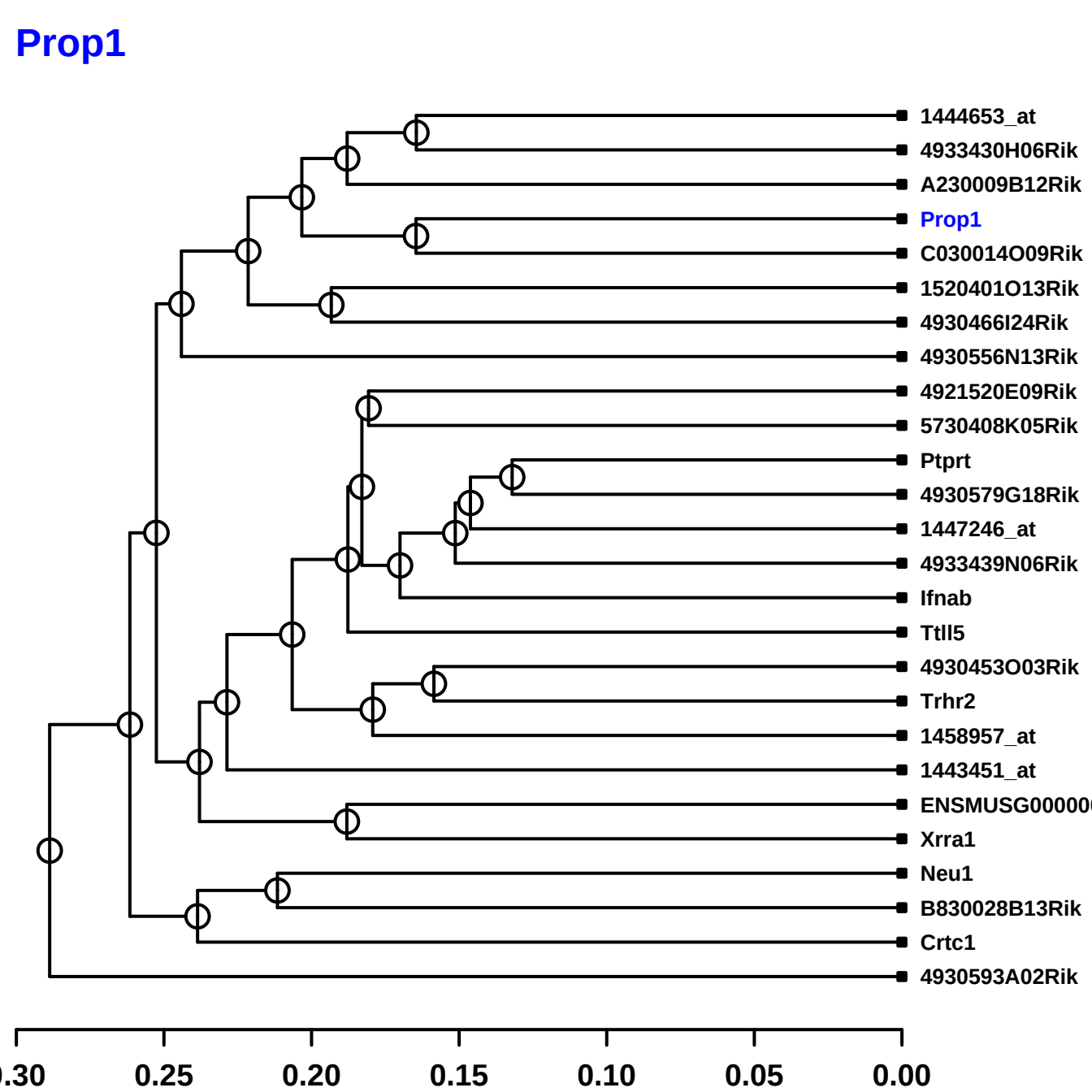

Developmental Series
Shc1
Kl
Insr
Adcy5
Prop1
Irs1
Ghrhr
Gpx4
Clk1
Surf1
Ghr
Ucp2
Igf1r
Pit1
PappA
Irs2
0.75
0.80
0.85
0.90
Local Connectivity Index ($\bar{r}_{10}$)


Treatment Series
Insr
Ucp2
Prop1
Ghrhr
PappA
Clk1
Irs1
Shc1
Adcy5
Gpx4
Igf1r
Kl
Ghr
Pit1
Surf1
Irs2
0.70
0.75
0.80
0.85
0.90
0.95
Local Connectivity Index ($\bar{r}_{10}$)


Mutation Series
Insr
Kl
Ghrhr
Prop1
Gpx4
Clk1
Shc1
PappA
Adcy5
Pit1
Ucp2
Ghr
Igf1r
Irs1
Irs2
Surf1
0.70
0.75
0.80
0.85
0.90
Local Connectivity Index ($\bar{r}_{10}$)

Section IV: Cluster Analyses

The next pages display dendrograms based on each of 16 lifespan−associated genes and their respective nearest−neighbors in the genome−wide transcriptional network. For each gene, the 25 most similar genes throughout the genome were identified based upon expression patterns from four independent datasets (Tissue, Developmental, Treatment and Mutation Series). Similarity between genes was determined by averaging absolute correlation coefficients across the four datasets. Each lifespan−associated gene was then clustered along with its neighbors to obtain the dendrograms shown in this file. In each image, the lifespan−associated gene upon which the dendrogram is based is shown in the upper−left corner. Throughout all images, the 16 lifespan−associated genes of interest have blue labels.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A230009B12Rik
Prop1
C030014O09Rik
1520401O13Rik
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4930556N13Rik
4921520E09Rik
5730408K05Rik
Ptprt
4930579G18Rik
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Ifnab
Ttll5
4930453O03Rik
Trhr2
1458957_at
1443451_at
ENSMUSG00000
Xrra1
Neu1
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Crtc1
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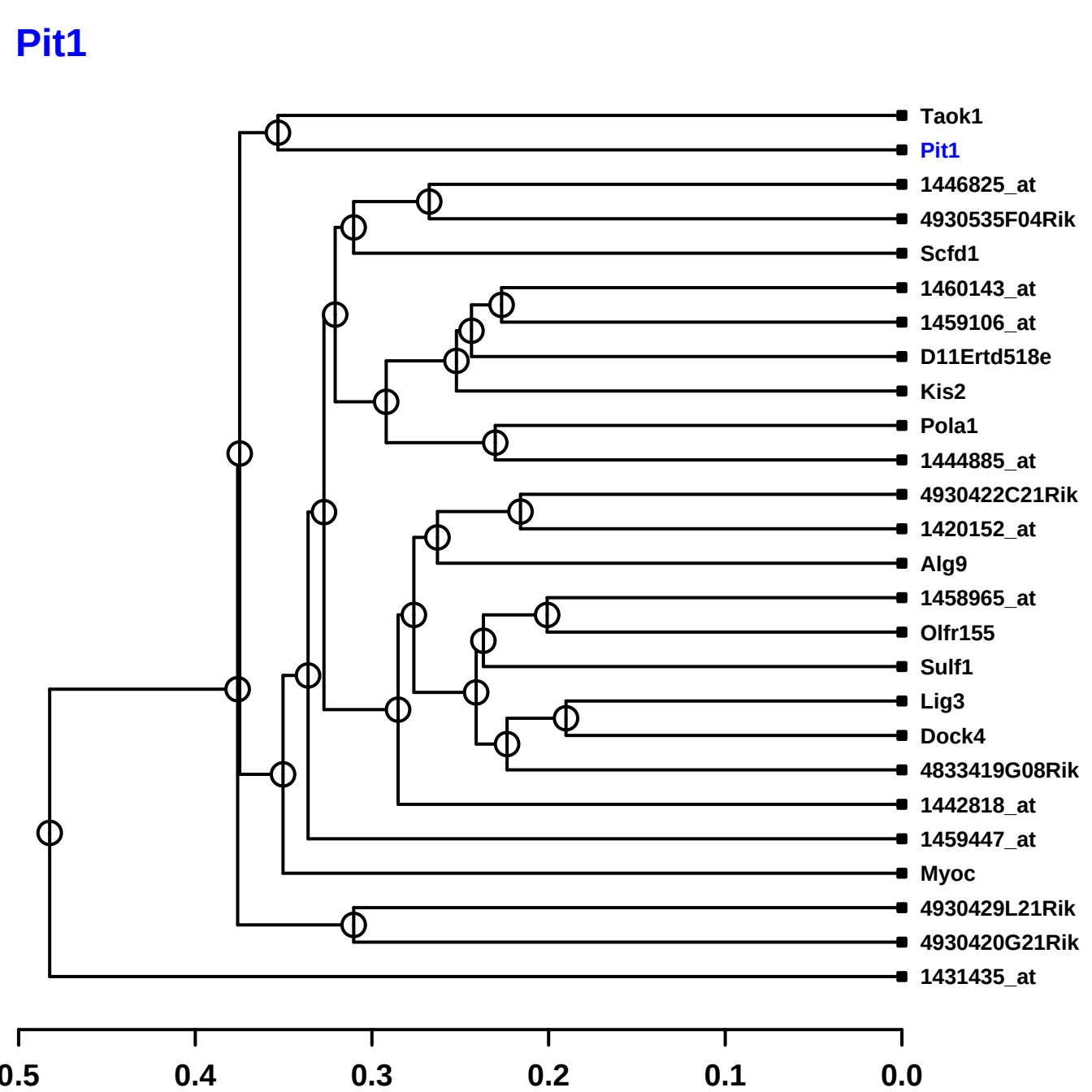
0.30
0.25
0.20
0.15
0.10
0.05
0.00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Taok1
Pit1
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Scfd1
1460143_at
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D11Ertd518e
Kis2
Pola1
1444885_at
4930422C21Rik
1420152_at
Alg9
1458965_at
Olfr155
Sulf1
Lig3
Dock4
4833419G08Rik
1442818_at
1459447_at
Myoc
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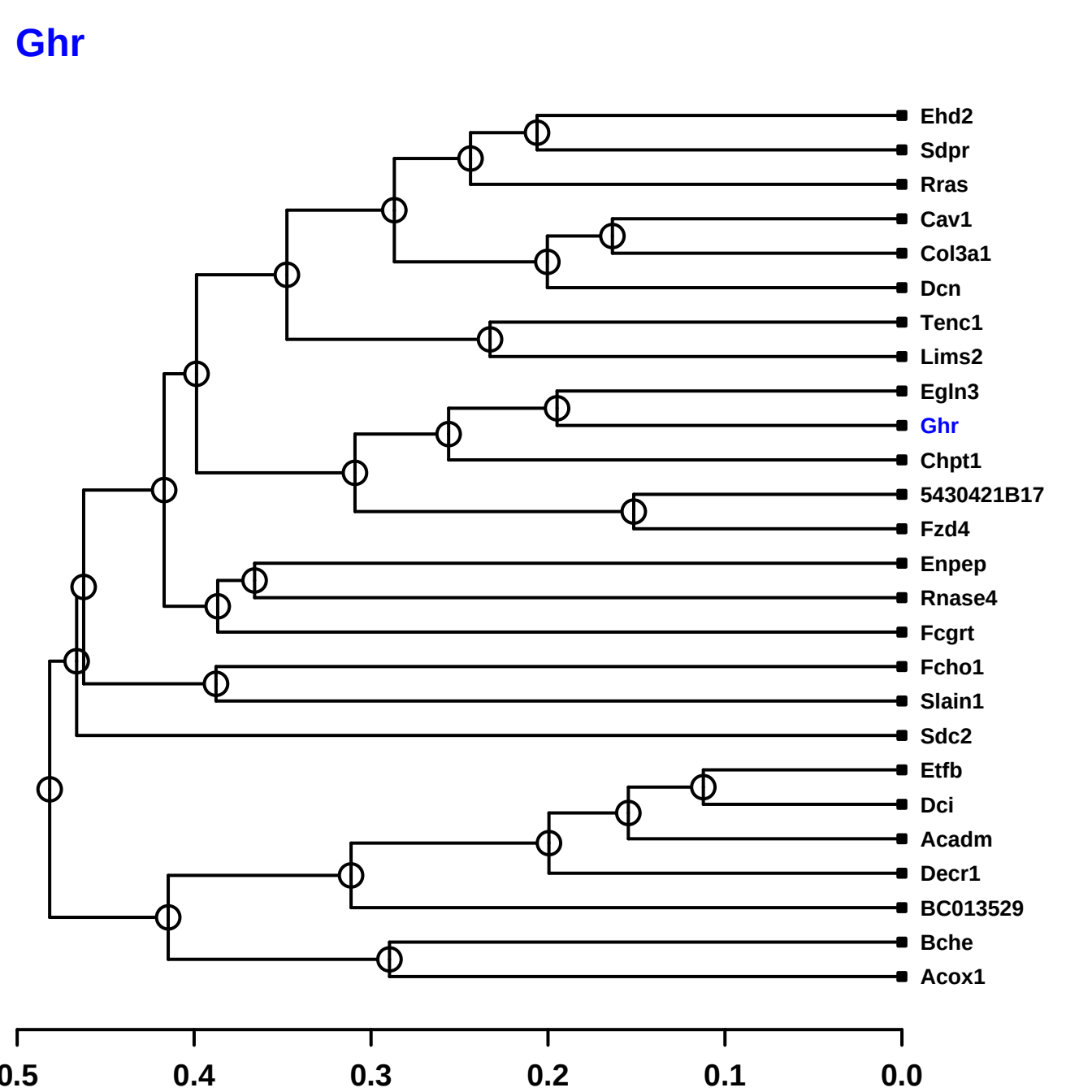
0.4
0.3
0.2
0.1
0.0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Ehd2
Sdpr
Rras
Cav1
Col3a1
Dcn
Tenc1
Lims2
Egln3
Ghr
Chpt1
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Fzd4
Enpep
Rnase4
Fcgrt
Fcho1
Slain1
Sdc2
Etfb
Dci
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Decr1
BC013529
Bche
Acox1
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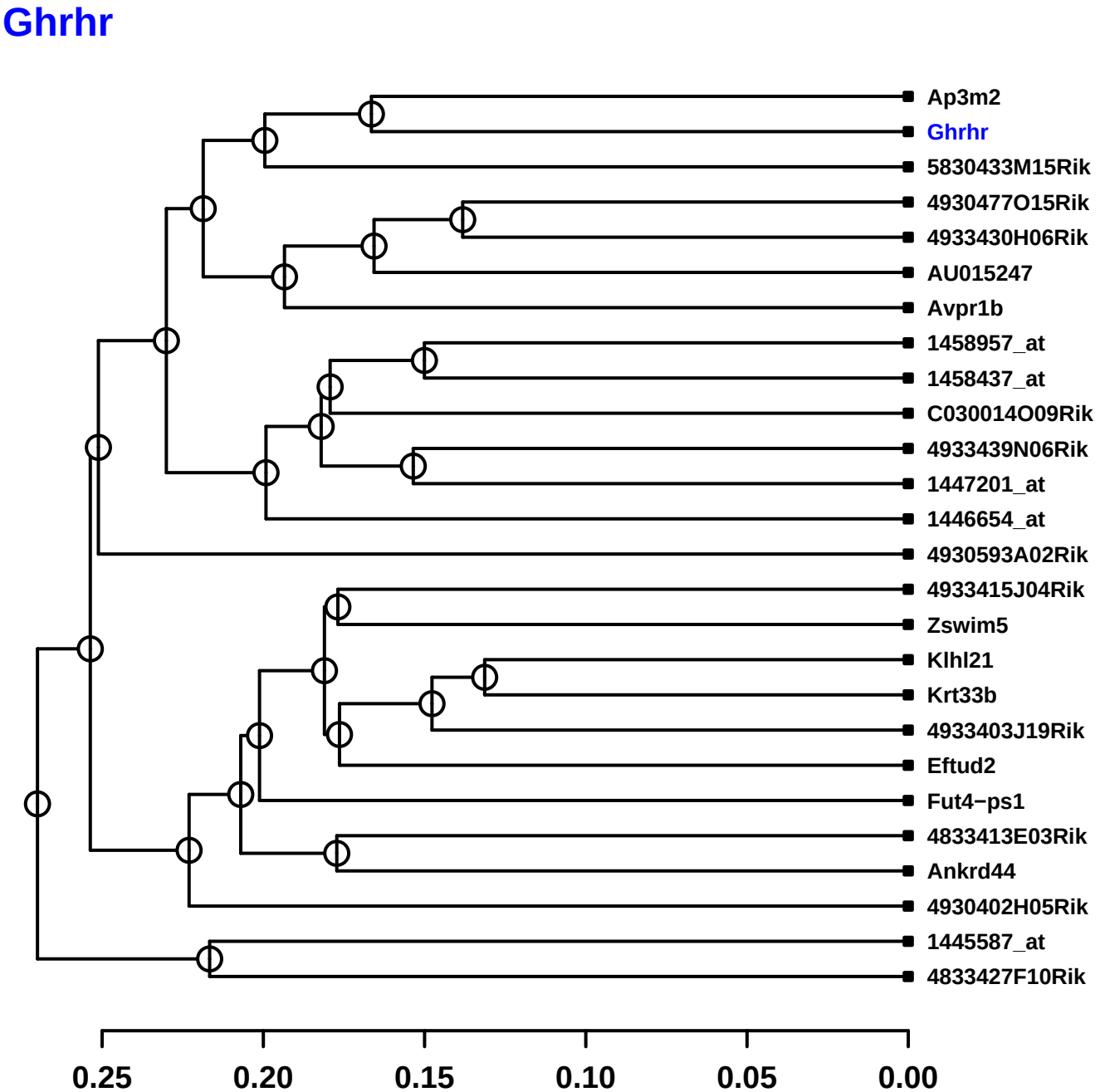
0.4
0.3
0.2
0.1
0.0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Ghrhr
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4930477O15Rik
4933430H06Rik
AU015247
Avpr1b
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1458437_at
C030014O09Rik
4933439N06Rik
1447201_at
1446654_at
4930593A02Rik
4933415J04Rik
Zswim5
Klhl21
Krt33b
4933403J19Rik
Eftud2
Fut4−ps1
4833413E03Rik
Ankrd44
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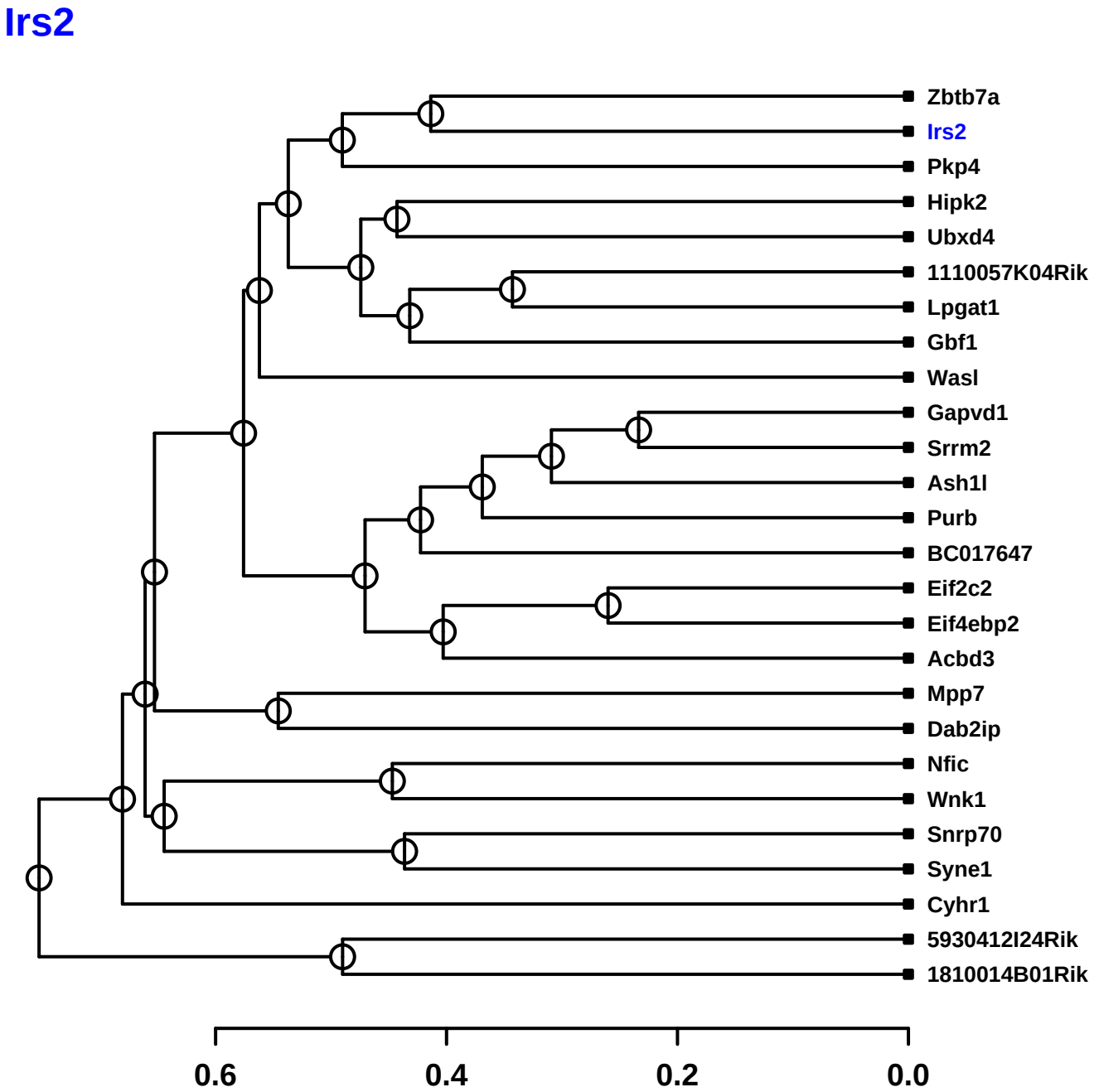
0.25
0.20
0.15
0.10
0.05
0.00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Zbtb7a
Irs2
Pkp4
Hipk2
Ubxd4
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Lpgat1
Gbf1
Wasl
Gapvd1
Srrm2
Ash1l
Purb
BC017647
Eif2c2
Eif4ebp2
Acbd3
Mpp7
Dab2ip
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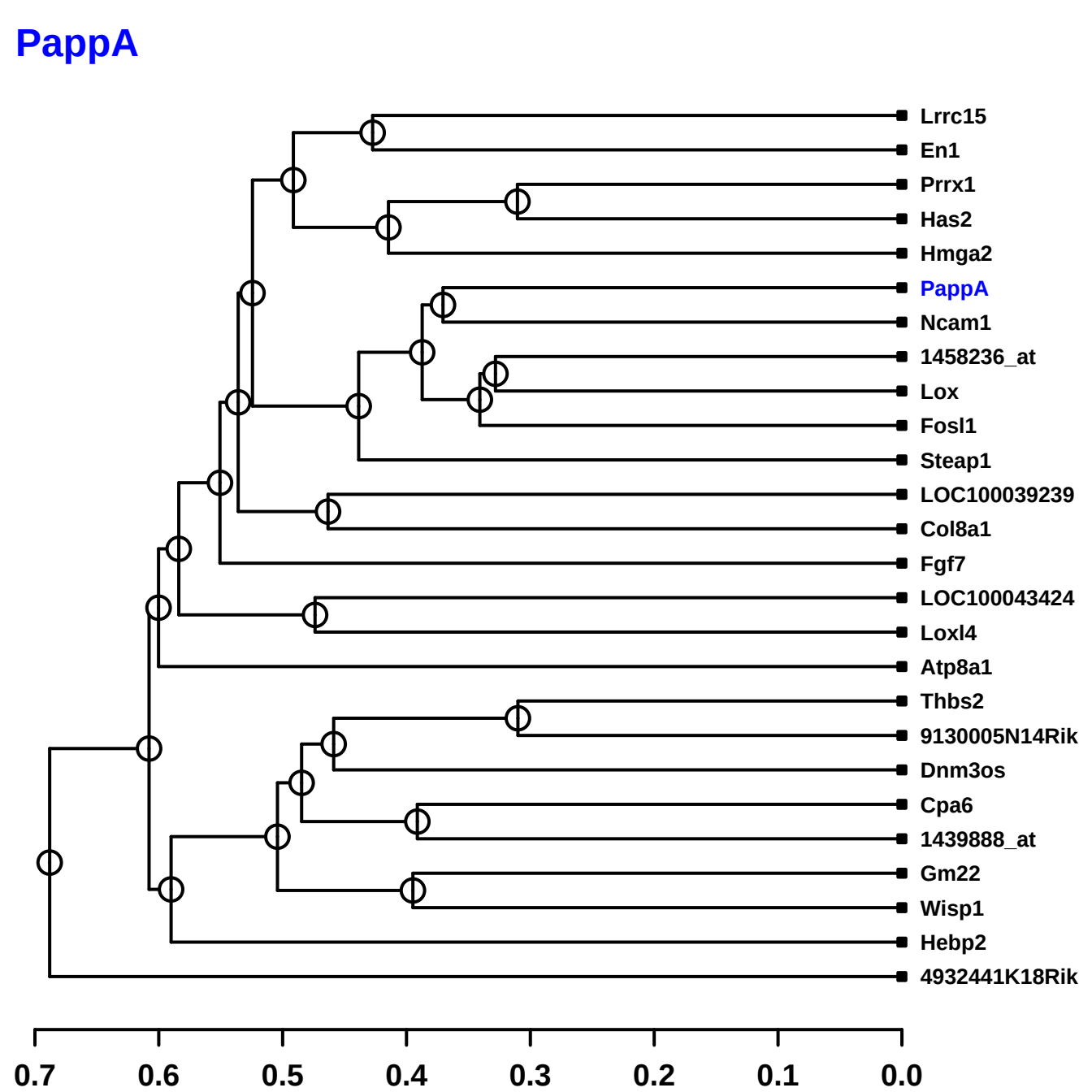
0.4
0.2
0.0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Prrx1
Has2
Hmga2
PappA
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Steap1
LOC100039239
Col8a1
Fgf7
LOC100043424
Loxl4
Atp8a1
Thbs2
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Dnm3os
Cpa6
1439888_at
Gm22
Wisp1
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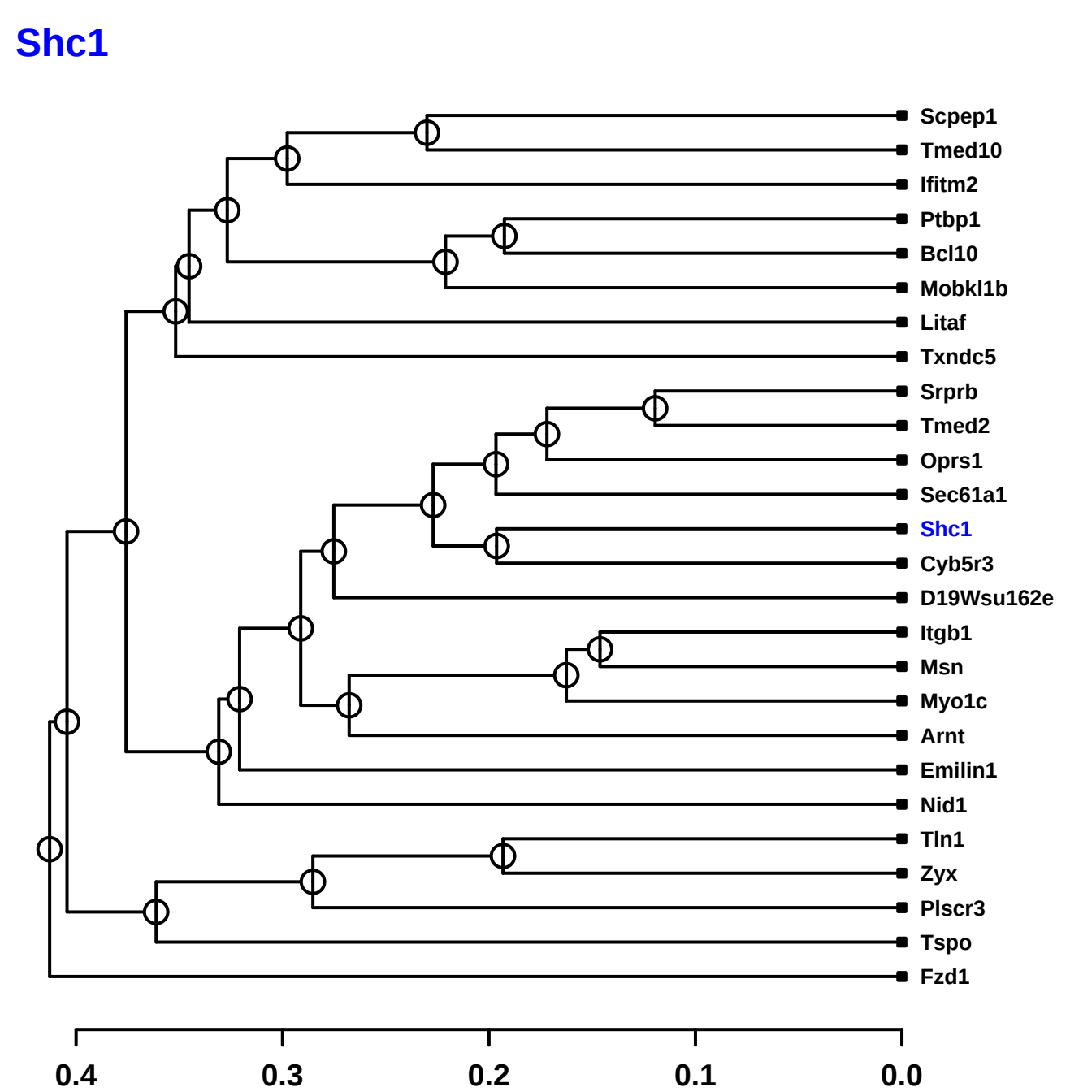
0.5
0.4
0.3
0.2
0.1
0.0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Scpep1
Tmed10
Ifitm2
Ptbp1
Bcl10
Mobkl1b
Litaf
Txndc5
Srprb
Tmed2
Oprs1
Sec61a1
Shc1
Cyb5r3
D19Wsu162e
Itgb1
Msn
Myo1c
Arnt
Emilin1
Nid1
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Plscr3
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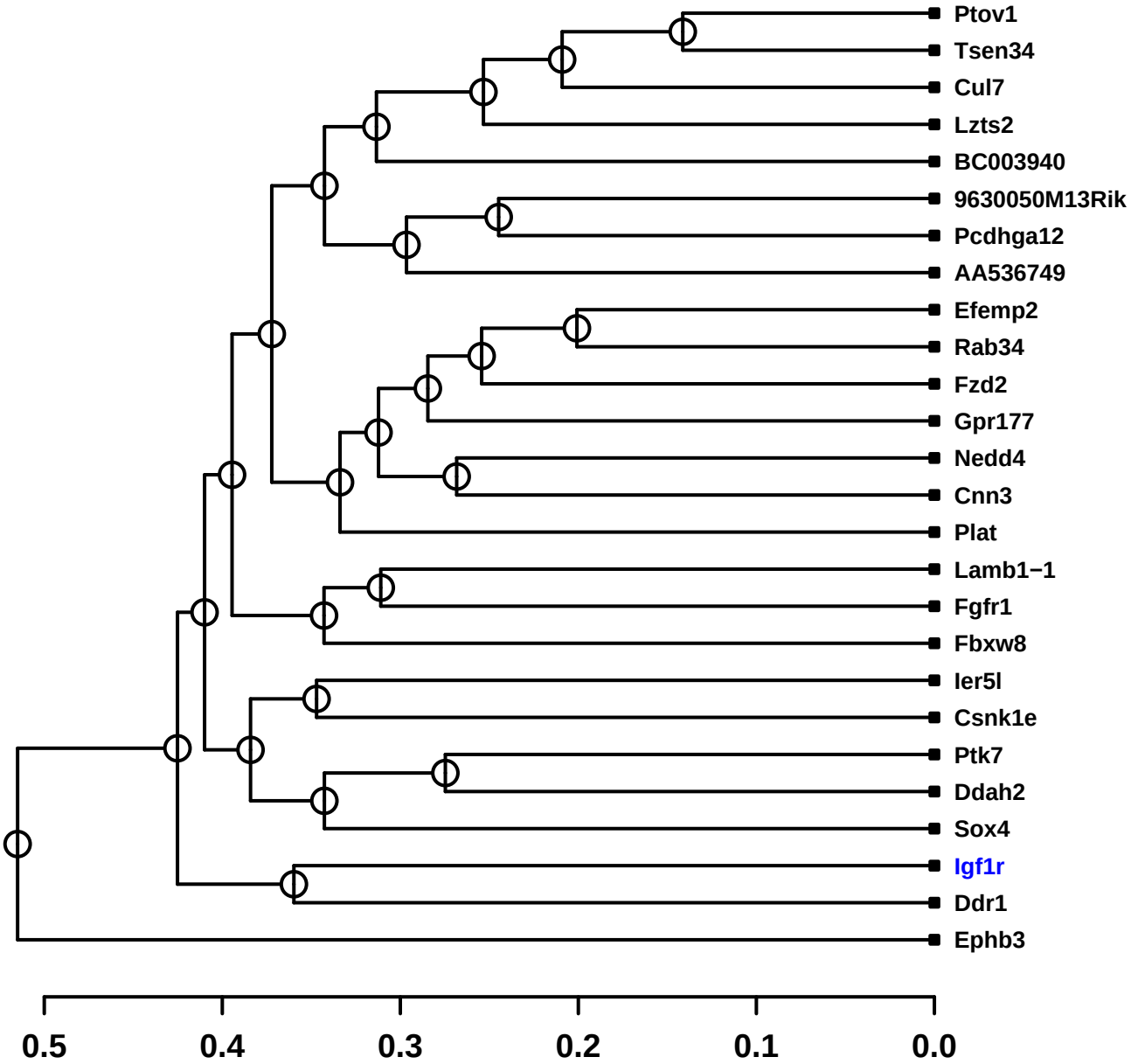
Igf1r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Cul7
Lzts2
BC003940
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Efemp2
Rab34
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Gpr177
Nedd4
Cnn3
Plat
Lamb1−1
Fgfr1
Fbxw8
Ier5l
Csnk1e
Ptk7
Ddah2
Sox4
Igf1r
Ddr1
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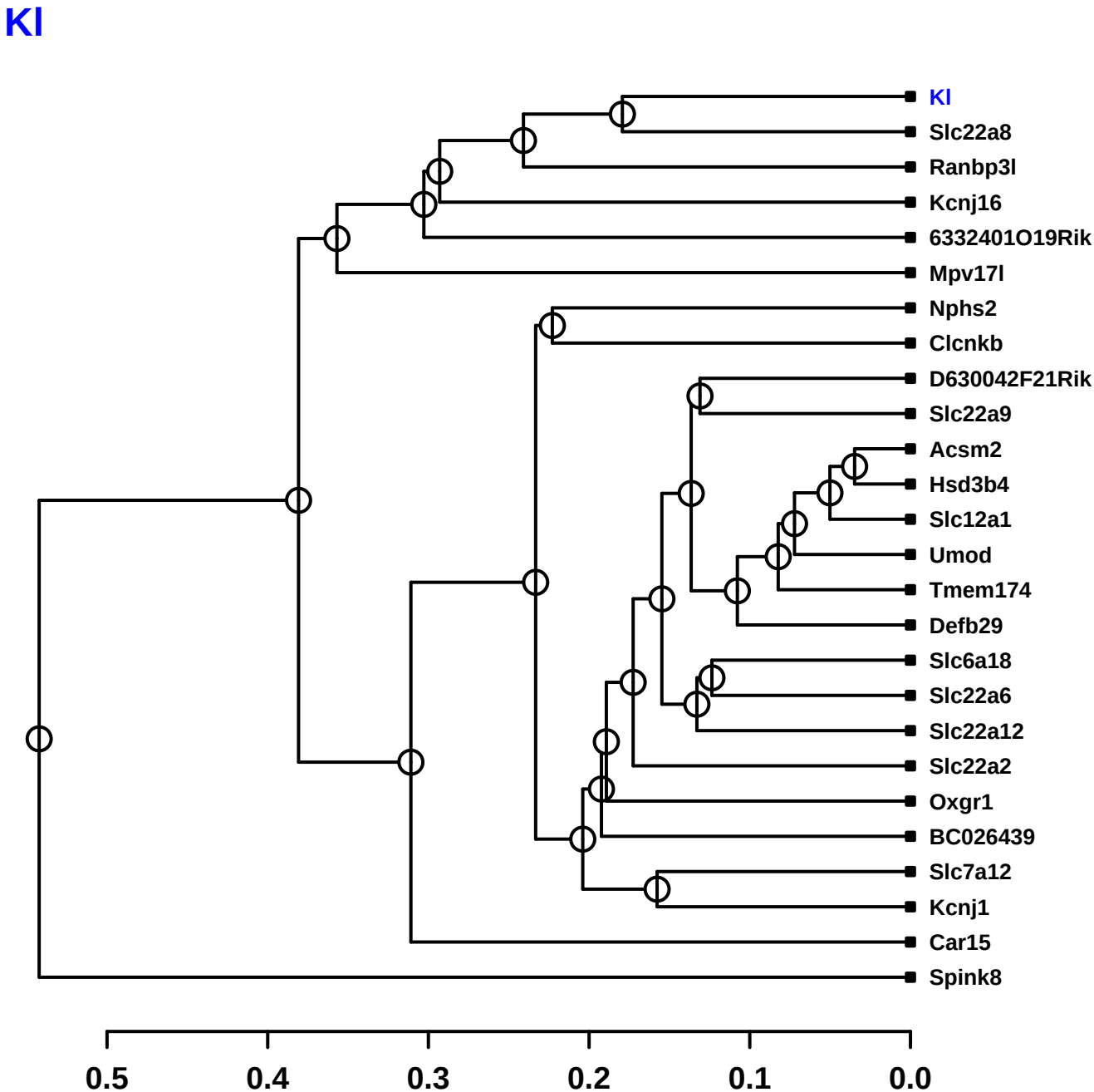
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Kcnj16
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Clcnkb
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Hsd3b4
Slc12a1
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Defb29
Slc6a18
Slc22a6
Slc22a12
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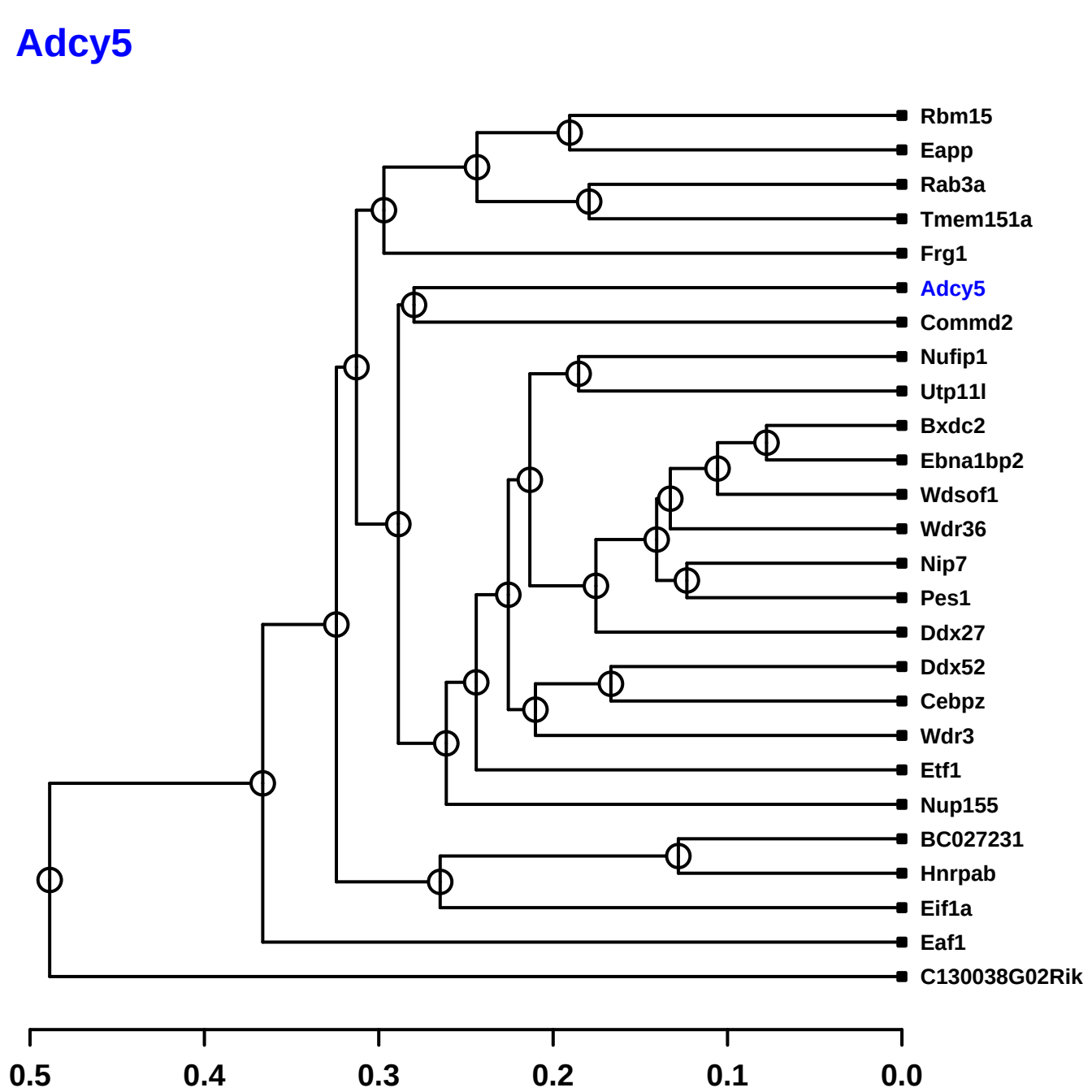
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Rbm15
Eapp
Rab3a
Tmem151a
Frg1
Adcy5
Commd2
Nufip1
Utp11l
Bxdc2
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Wdsof1
Wdr36
Nip7
Pes1
Ddx27
Ddx52
Cebpz
Wdr3
Etf1
Nup155
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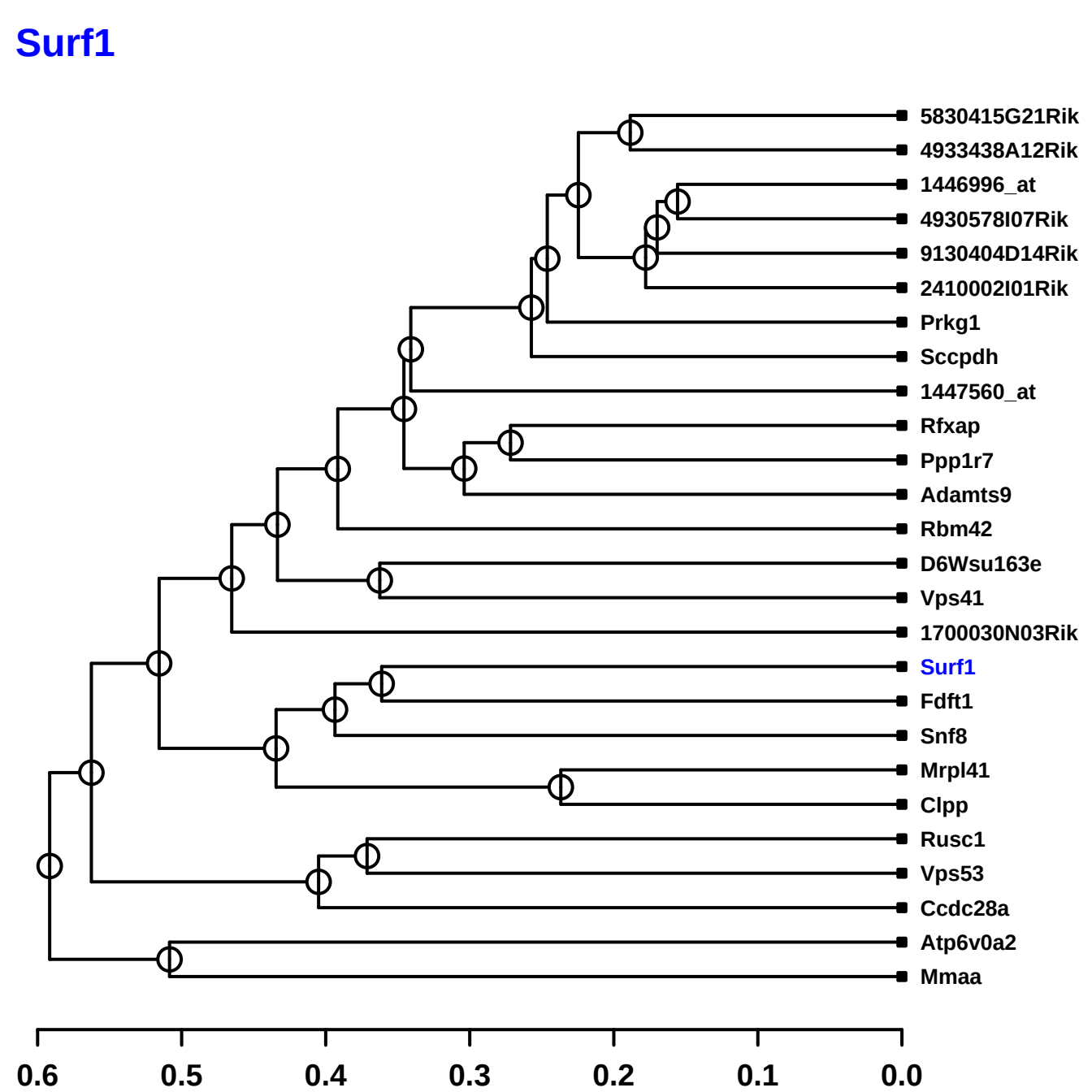
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4933438A12Rik
1446996_at
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9130404D14Rik
2410002I01Rik
Prkg1
Sccpdh
1447560_at
Rfxap
Ppp1r7
Adamts9
Rbm42
D6Wsu163e
Vps41
1700030N03Rik
Surf1
Fdft1
Snf8
Mrpl41
Clpp
Rusc1
Vps53
Ccdc28a
Atp6v0a2
Mmaa
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0.4
0.3
0.2
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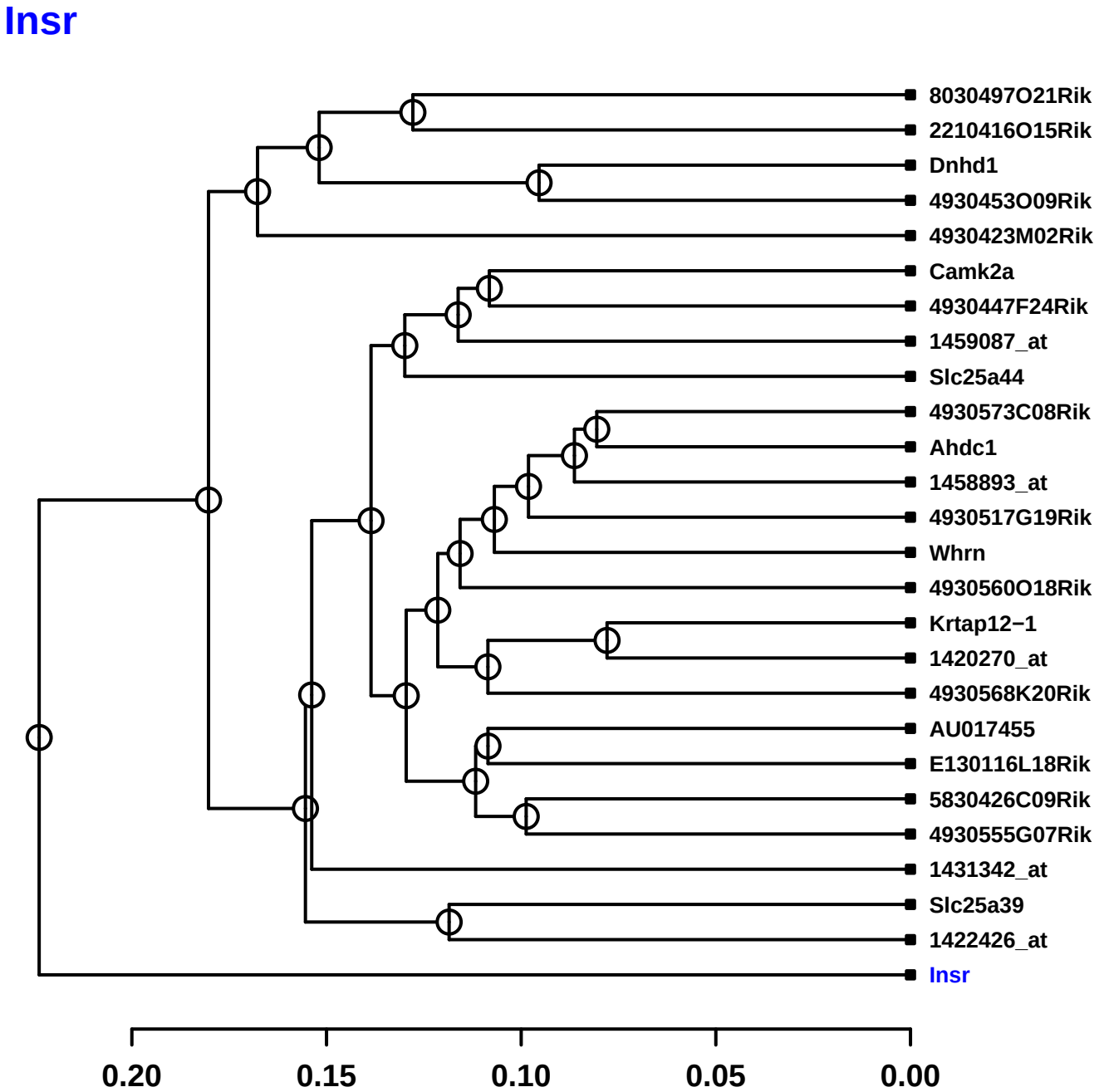
0.0


Insr
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Dnhd1
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Camk2a
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Slc25a44
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Ahdc1
1458893_at
4930517G19Rik
Whrn
4930560O18Rik
Krtap12−1
1420270_at
4930568K20Rik
AU017455
E130116L18Rik
5830426C09Rik
4930555G07Rik
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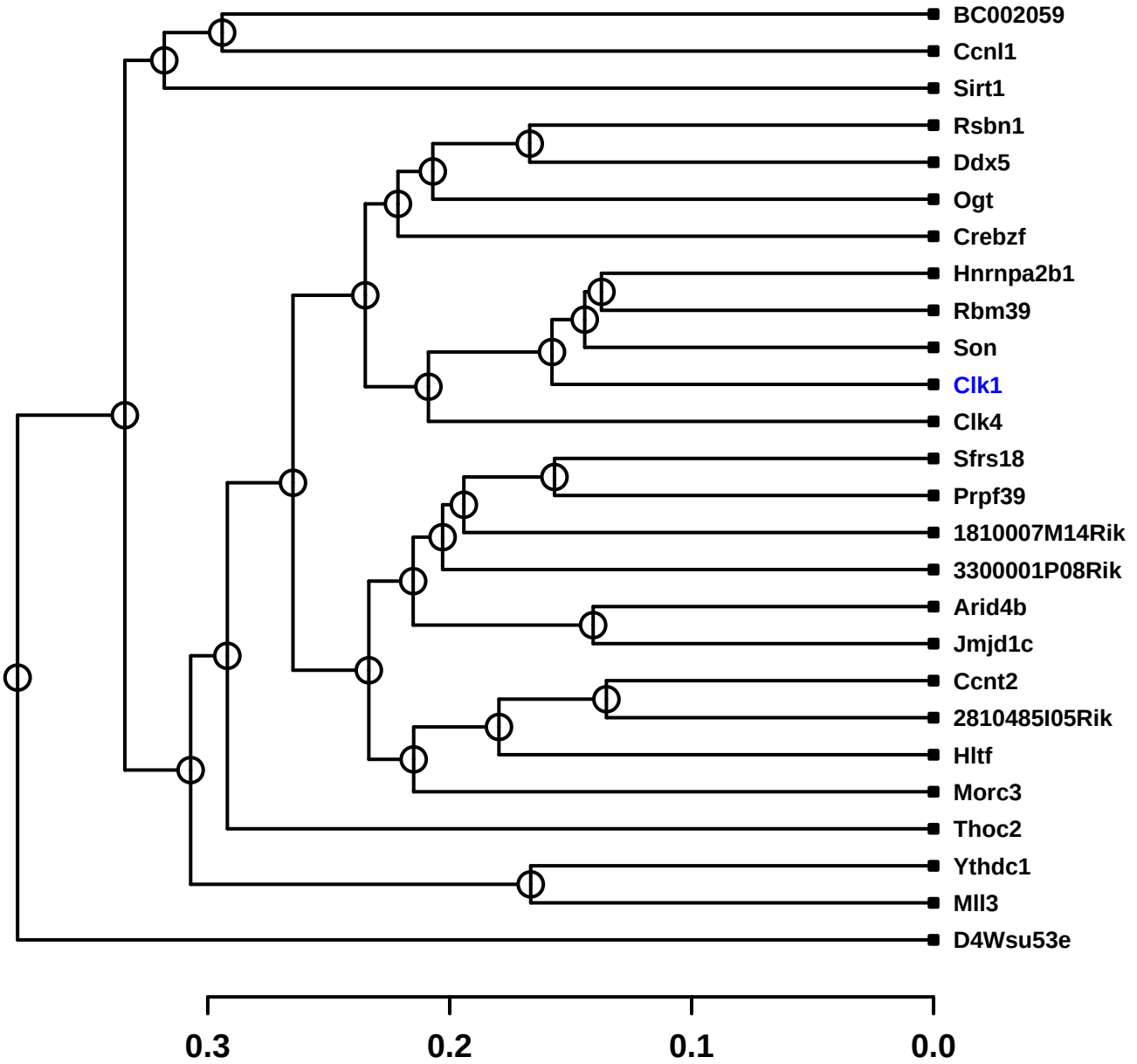
0.05
0.00

Clk1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Sirt1
Rsbn1
Ddx5
Ogt
Crebzf
Hnrnpa2b1
Rbm39
Son
Clk1
Clk4
Sfrs18
Prpf39
1810007M14Rik
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Arid4b
Jmjd1c
Ccnt2
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Hltf
Morc3
Thoc2
Ythdc1
Mll3
D4Wsu53e
0.3
0.2
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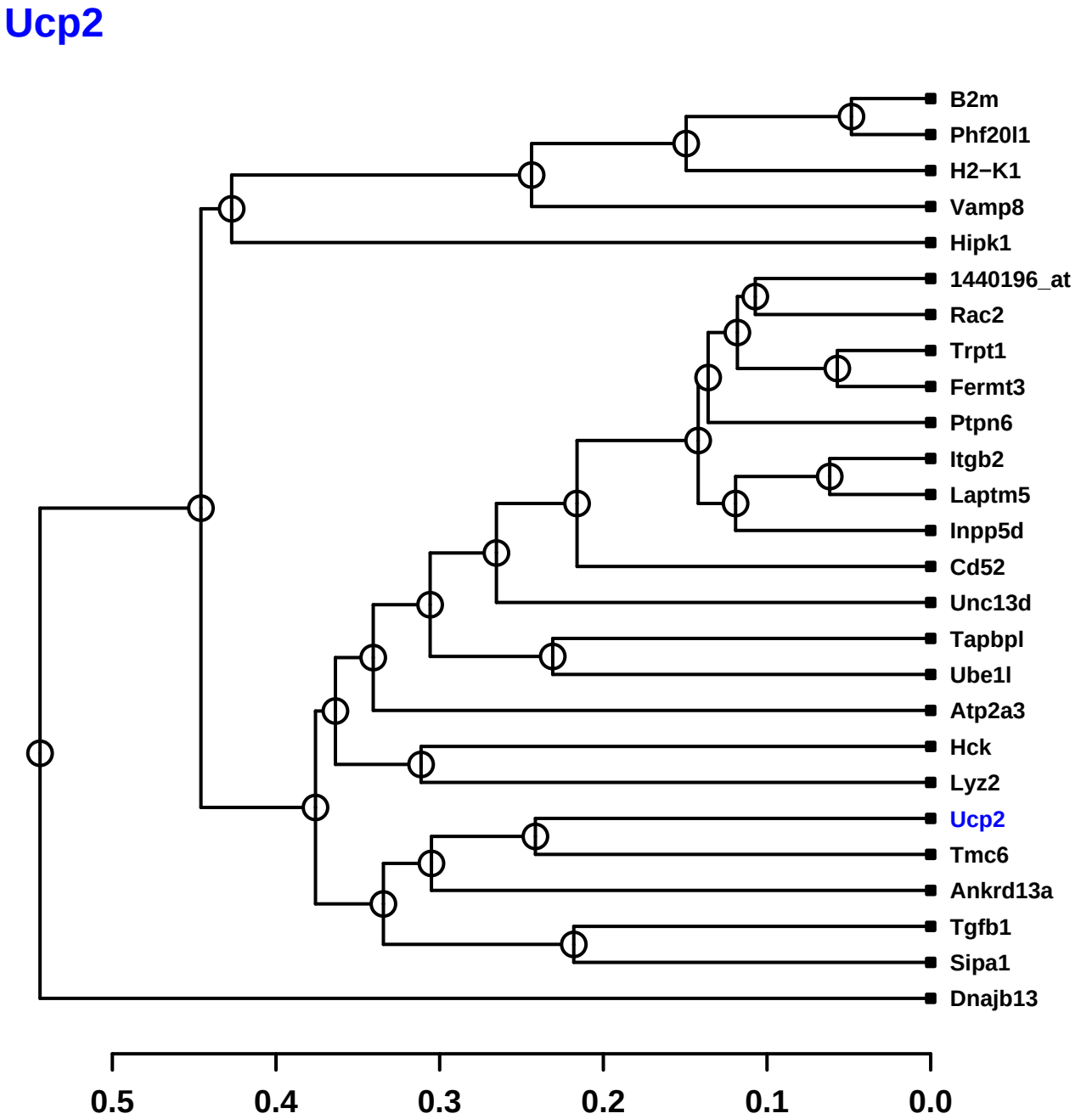
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H2−K1
Vamp8
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Fermt3
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Itgb2
Laptm5
Inpp5d
Cd52
Unc13d
Tapbpl
Ube1l
Atp2a3
Hck
Lyz2
Ucp2
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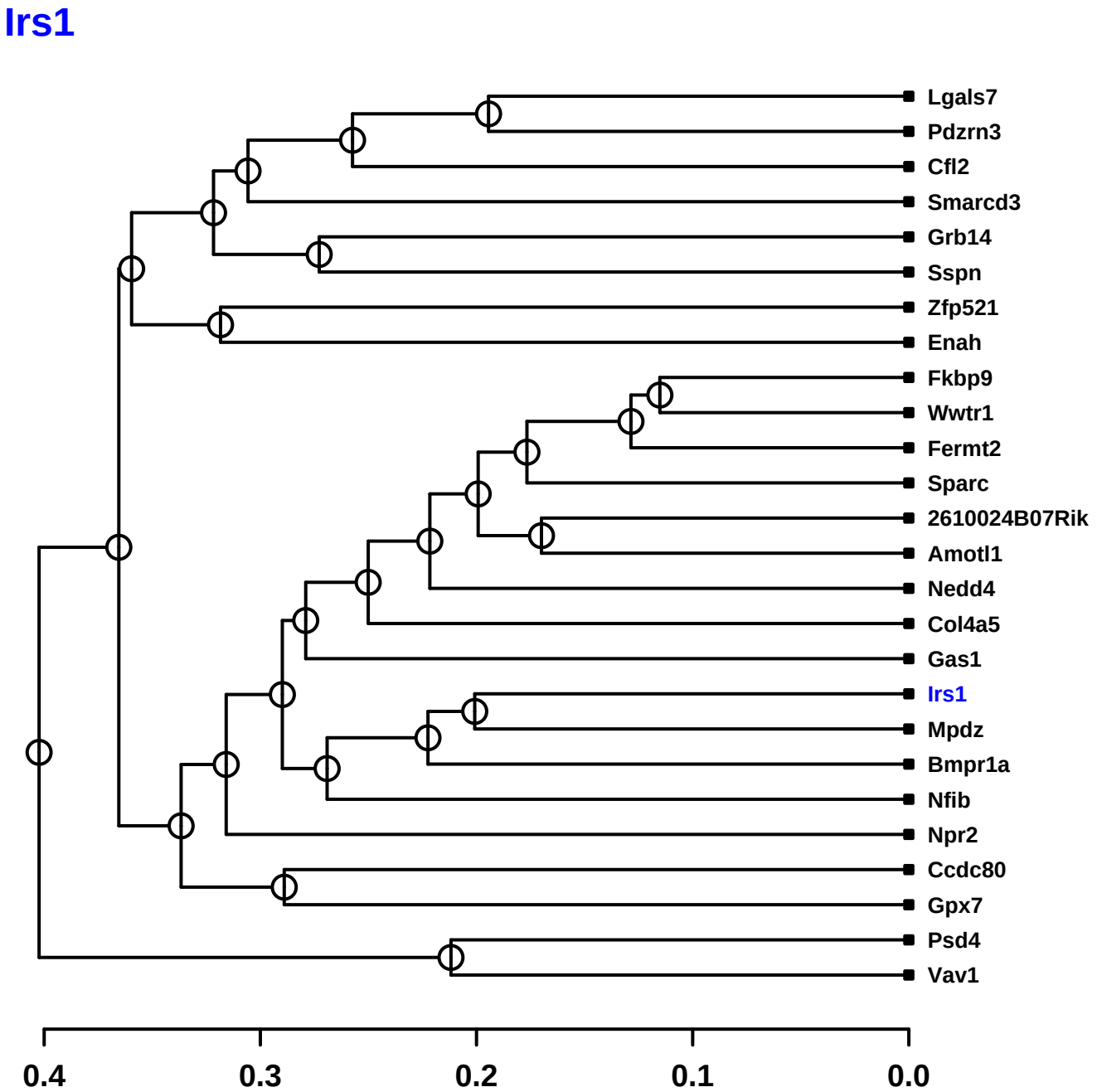
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Cfl2
Smarcd3
Grb14
Sspn
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Enah
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Wwtr1
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Sparc
2610024B07Rik
Amotl1
Nedd4
Col4a5
Gas1
Irs1
Mpdz
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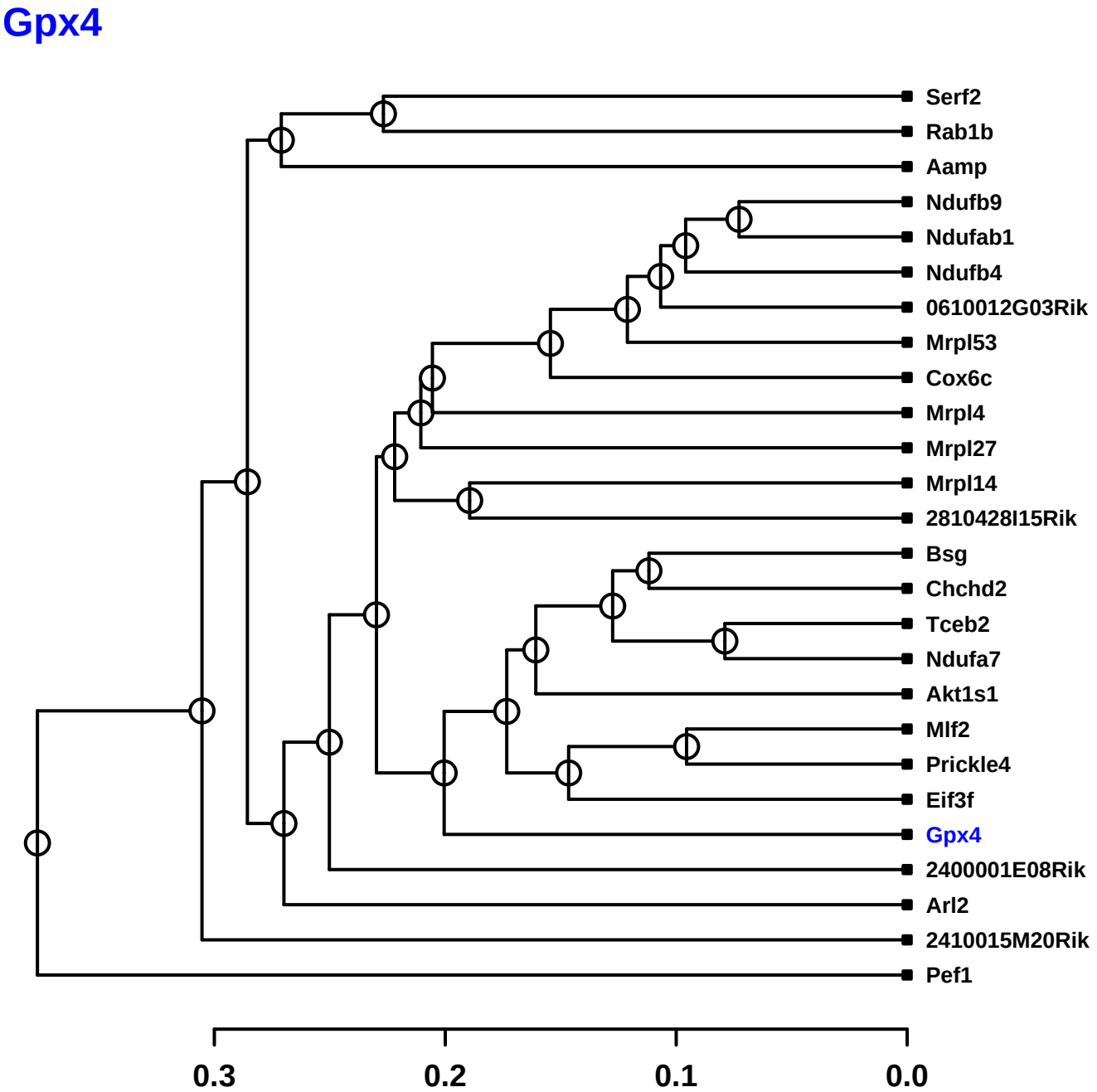
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Mrpl27
Mrpl14
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Bsg
Chchd2
Tceb2
Ndufa7
Akt1s1
Mlf2
Prickle4
Eif3f
Gpx4
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Arl2
2410015M20Rik
Pef1
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0.1
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