

# Design

- Used GENCODE V29 (hg38) as annotation
- Split genes by biotypes:
  - protein\_coding
  - lincRNAs
  - miRNA
  - Ribozyme
  - snoRNA
  - snRNA
  - scaRNA
  - misc\_RNA
- Extended exons by 20bp on each side
- Picked all guides within the extended exons for each gene (so that the site 12-16bp from the PAM is within the extended exon)

## Top 10 growth genes

#genesymbol	totalSNPs	nClinvarBenignSNPs	nClinvarPathogenicSNPs	nClinvarTotal
POLG	8098	14	44	58
ACTA1	2499	0	39	39
BRCA2	22765	211	37	248
DKC1	3363	1	37	38
SOD1	1008	0	34	34
KIF1A	11741	3	30	33
SOS1	8792	11	29	40
DYNC1H1	30703	7	23	30
SDHB	1835	5	22	27
GNE	4966	1	21	22

#GeneID	Symbol	GeneInfo	Localization	Process	Function	# elements 1	casTLE Effect 1	casTLE Score 1	# elements 2	casTLE Effect 2	casTLE Score 2	Combo casTLE Effect	Combo casTLE Score	casTLE p-value	Minimum Effect Estimate	Maximum Effect Estimate
ACTA1	ACTA1	N/A	None	None	None	10	-6.1	19.6	10	-5.2	20	-6.1	38.8	0.0273	-11.5	-5.7
SOS1	SOS1	N/A	None	None	None	10	-0.8	11.6	10	-1.1	35.8	-1.1	46.4	0.0119	-1.4	-0.8
KIF1A	KIF1A	N/A	None	None	None	10	-3.4	20.8	10	-2.4	27.1	-3.3	45.7	0.013	-5.7	-2.8
POLG	POLG	N/A	None	None	None	10	-1.7	21.7	10	-1.3	33.9	-1.6	52.9	0.00552	-2.1	-1.2
DKC1	DKC1	N/A	None	None	None	10	-4.2	175	10	-4.8	124	-4.8	296	1.00E-05	-5.6	-4
SDHB	SDHB	N/A	None	None	None	10	-2	16.9	9	-2.5	35.3	-2.5	50.2	0.00758	-3.7	-1.8
BRCA2	BRCA2	N/A	None	None	None	10	-1.1	54.8	10	-1	55.4	-1.1	110	2.00E-05	-1.3	-0.9
DYNC1H1	DYNC1H1	N/A	None	None	None	10	-4.1	67.4	10	-3.3	90.1	-4	154	1.00E-05	-4.9	-3.2
GNE	GNE	N/A	None	None	None	10	-4.3	113	10	-3.2	135	-4.2	243	1.00E-05	-4.9	-3.4
SOD1	SOD1	N/A	None	None	None	10	-2.2	61	10	-2.3	104	-2.2	164	1.00E-05	-2.7	-1.9

All guides, i.e. CFD > 0.0

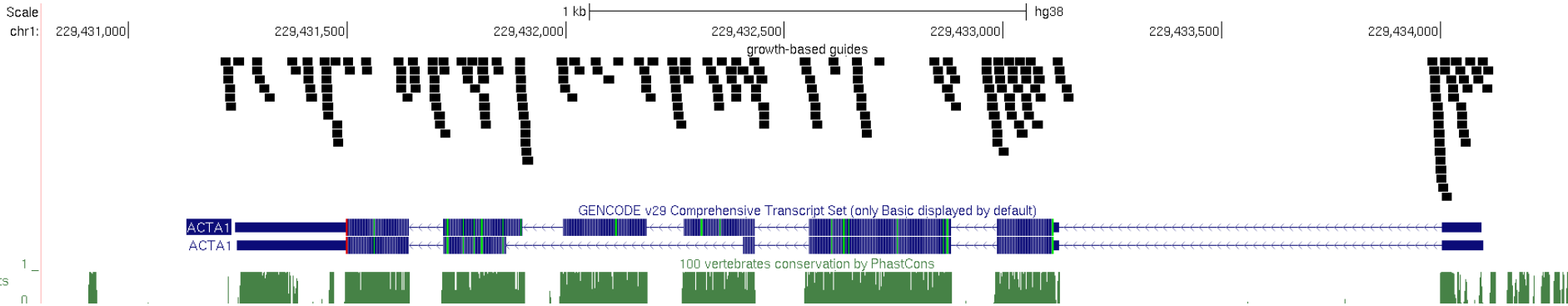
#gene	exons	total_length	total_guides_passing_CFD	fraction_of_bases_covered
ACTA1	11	1768	236	0.29638009
BRCA2	43	13404	778	0.184049537
DKC1	41	4788	522	0.300960735
DYNC1H1	167	39010	4122	0.29671879
GNE	26	6467	553	0.244008041
KIF1A	107	18957	3761	0.47618294
POLG	81	6912	1311	0.457899306
SDHB	19	2891	323	0.312348668
SOD1	10	2253	315	0.373280071
SOS1	38	10277	781	0.231390484

**Total guides: 12702**

All guides, i.e. CFD > 0.2

<u>#gene</u>	<u>exons</u>	<u>total_length</u>	<u>total_guides_passing_CFD</u>	<u>fraction_of_bases_covered</u>
ACTA1	11	1768	173	0.238122172
BRCA2	43	13404	437	0.1087735
DKC1	41	4788	357	0.219298246
DYNC1H1	167	39010	2733	0.211407331
GNE	26	6467	378	0.175506417
KIF1A	107	18957	2179	0.311019676
POLG	81	6912	871	0.335069444
SDHB	19	2891	220	0.227948807
SOD1	10	2253	234	0.286284953
SOS1	38	10277	477	0.151211443

**Total guides:                      8059**



Scale

chr13:

20 kb

hg38

32,320,000 | 32,325,000 | 32,330,000 | 32,335,000 | 32,340,000 | 32,345,000 | 32,350,000 | 32,355,000 | 32,360,000 | 32,365,000 | 32,370,000 | 32,375,000 | 32,380,000 | 32,385,000 | 32,390,000 | 32,395,000 | 32,400,000

growth-based guides

ZAR1L

BRCA2

BRCA2

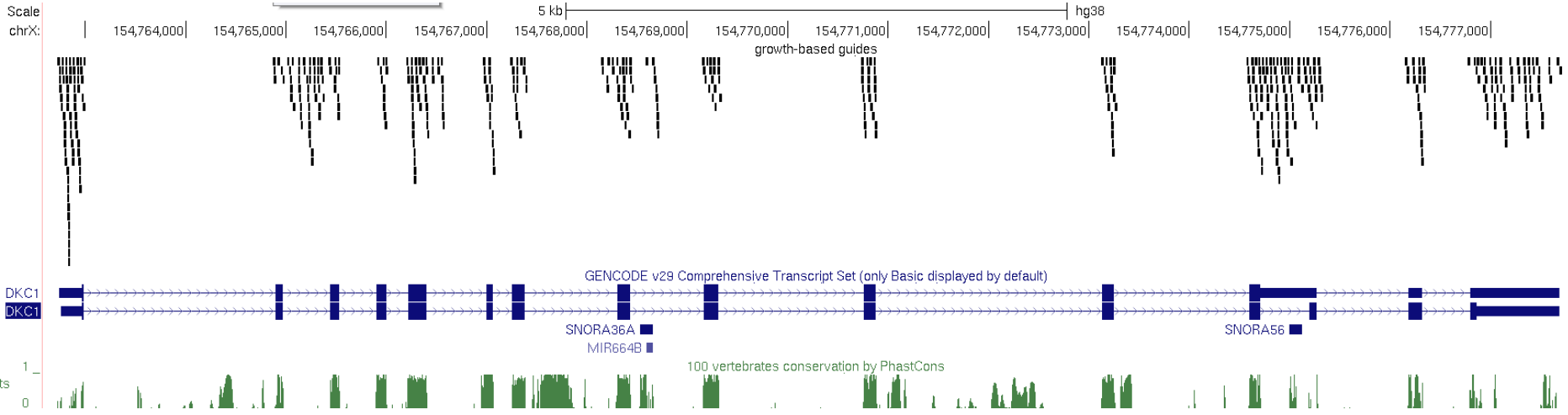
GENCODE v29 Comprehensive Transcript Set (only Basic displayed by default)

100 vertebrates conservation by PhastCons

Verts

1

0



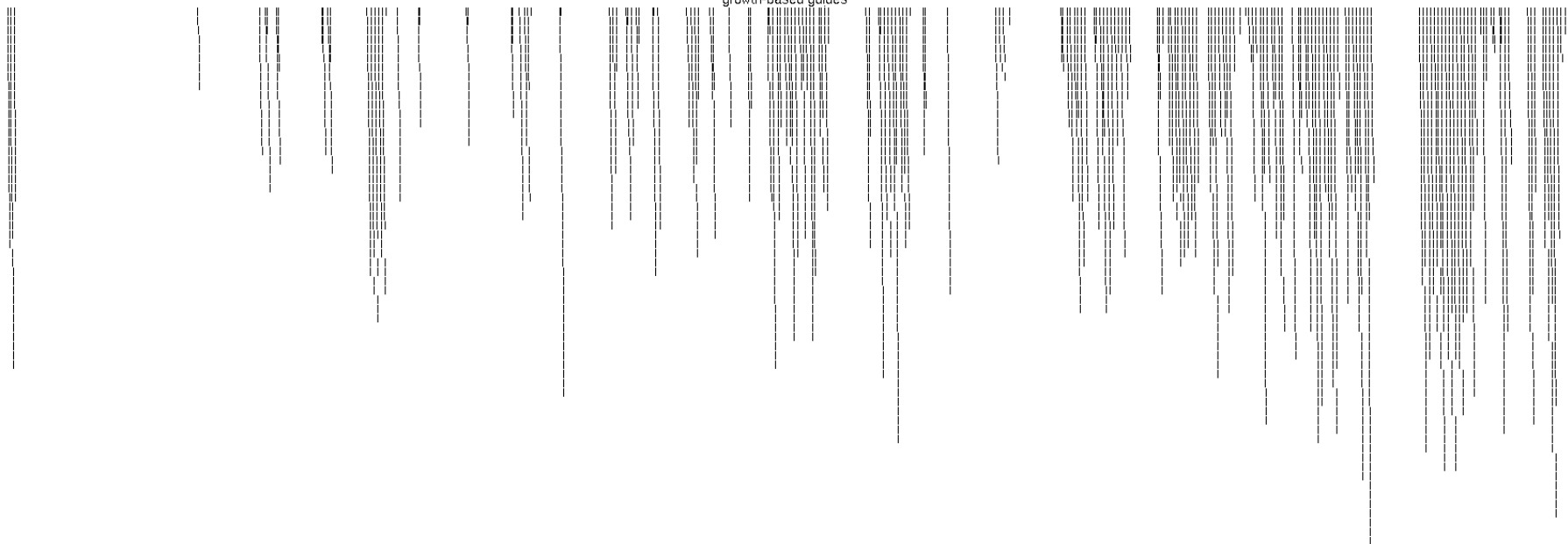
Scale

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20 kb

hg38

growth-based guides



GENCODE v29 Comprehensive Transcript Set (only Basic displayed by default)

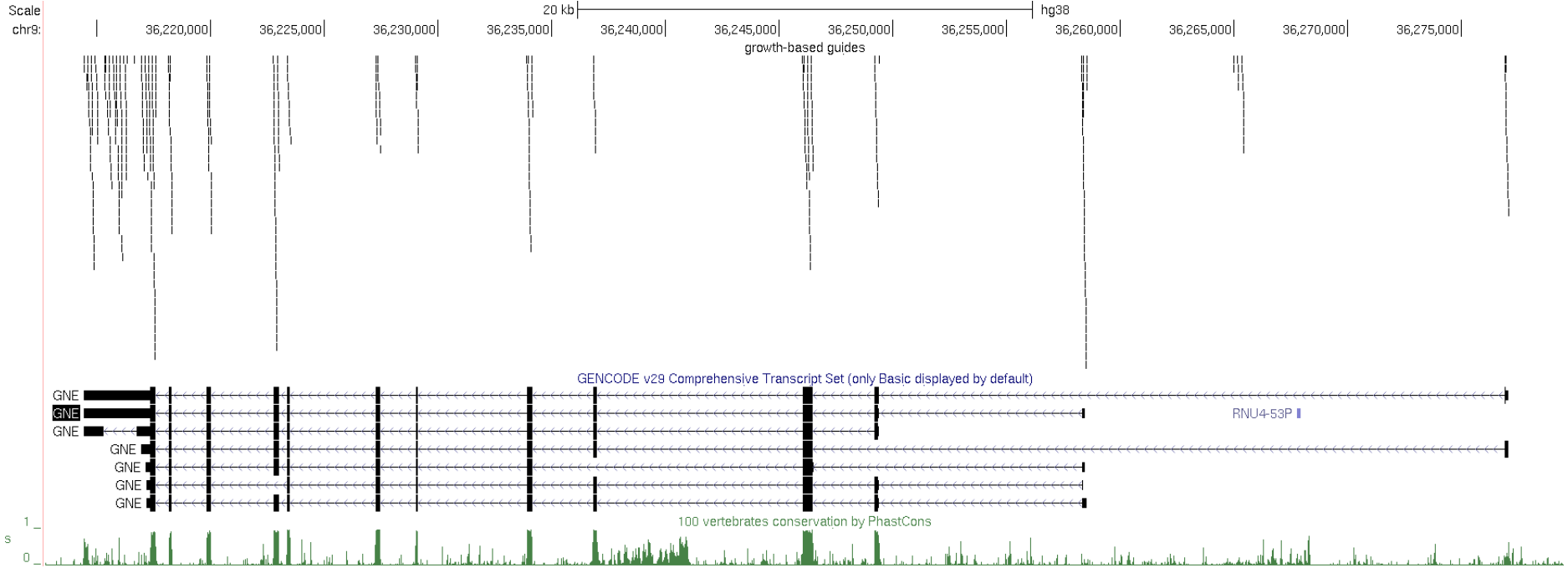
100 vertebrates conservation by PhastCons

DYNC1H1

1

0

Verts



Scale

chr2:

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240,730,000|

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240,760,000|

240,770,000|

240,780,000|

240,790,000|

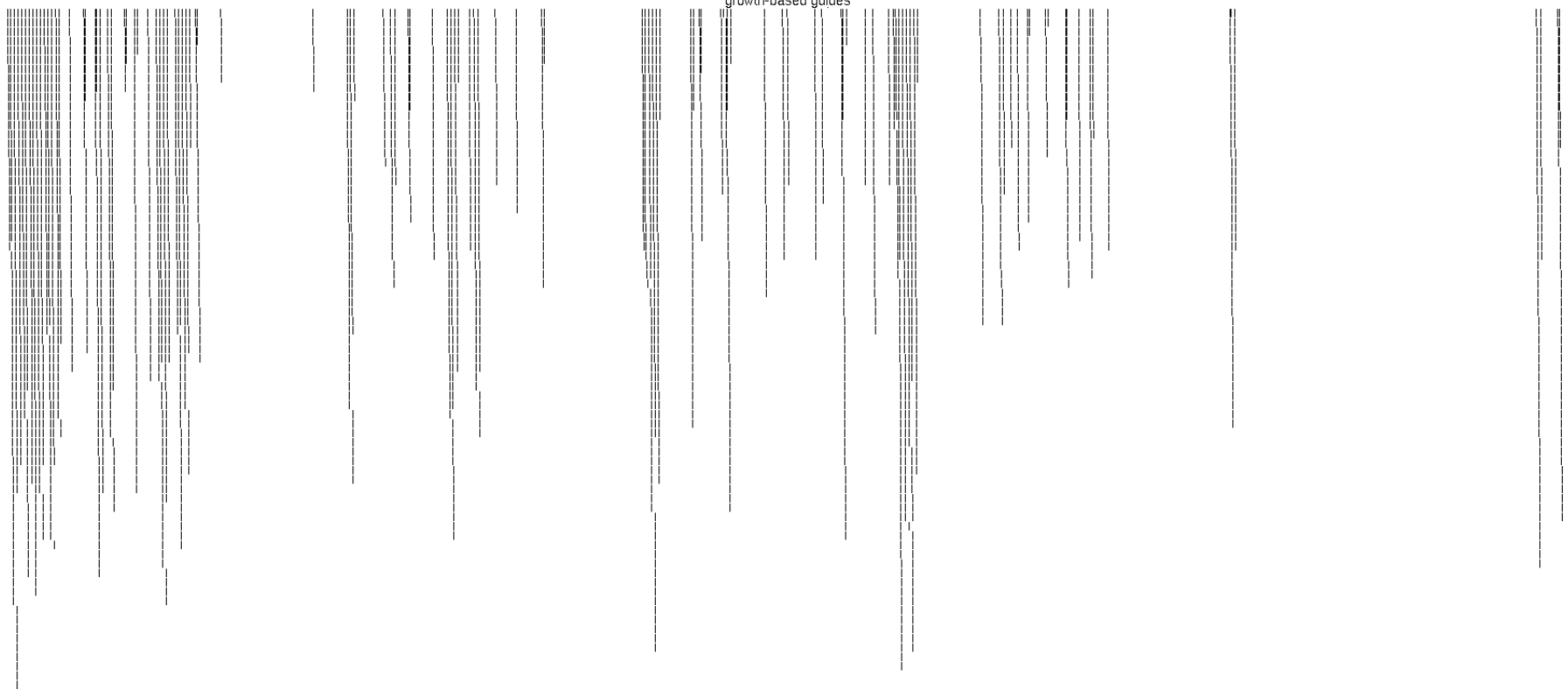
hg38

240,800,000|

240,810,000|

240,820,000|

growth-based guides



GENCODE v29 Comprehensive Transcript Set (only Basic displayed by default)

KIF1A

KIF1A

KIF1A

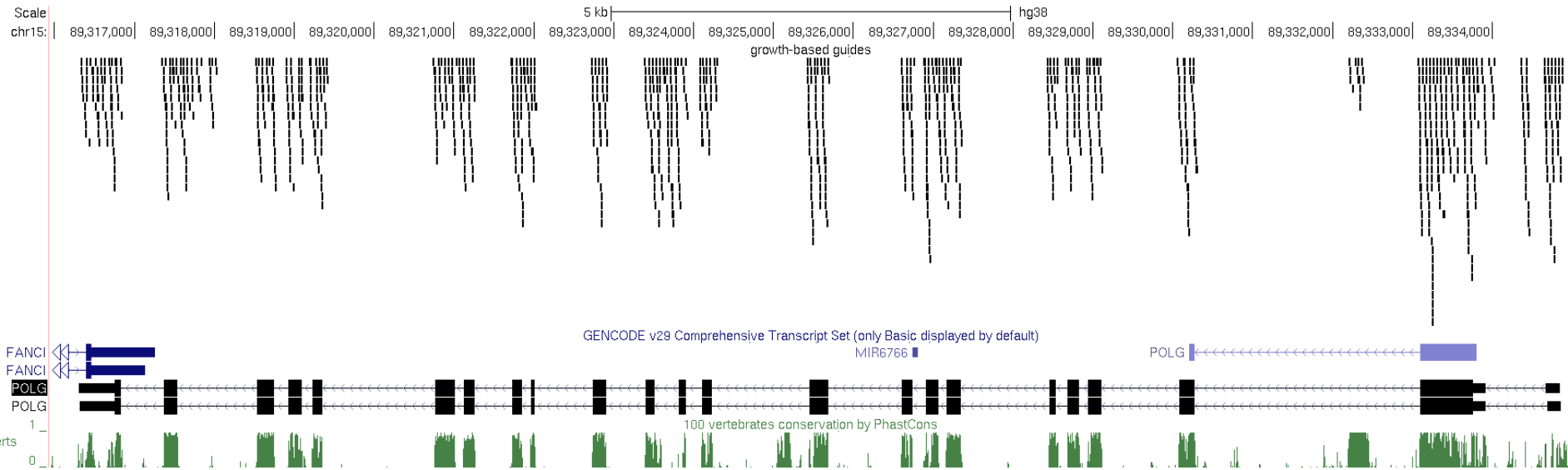
KIF1A

KIF1A

KIF1A

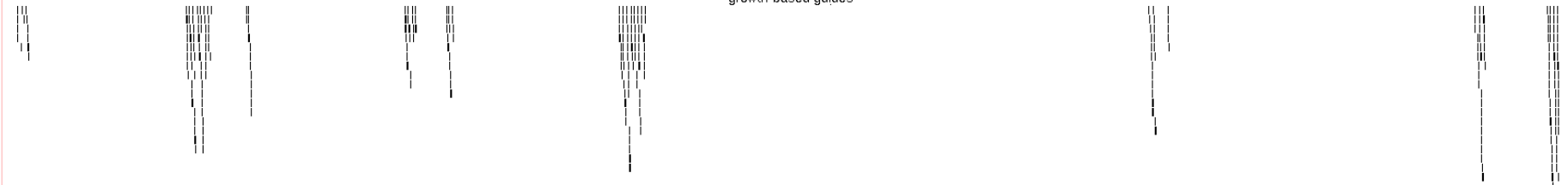
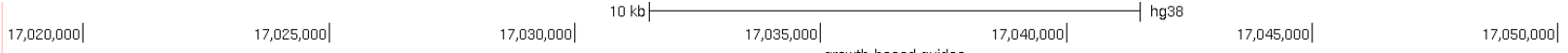
KIF1A

KIF1A



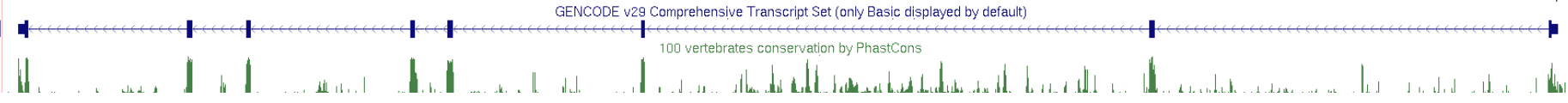
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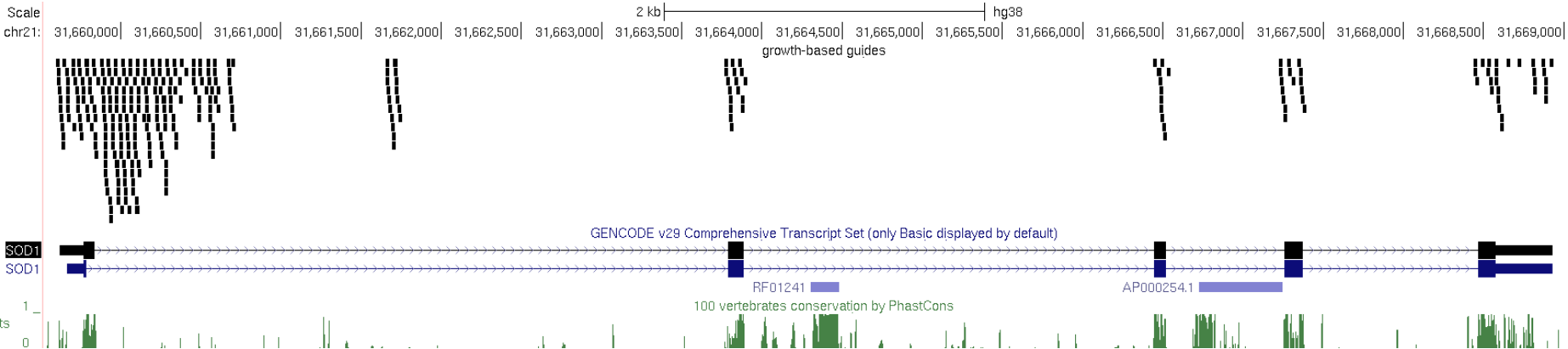
chr1:



SDHB

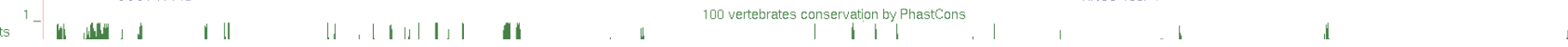
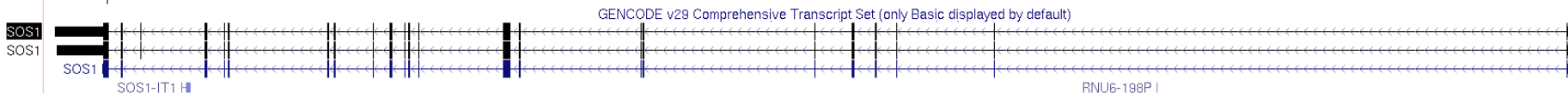
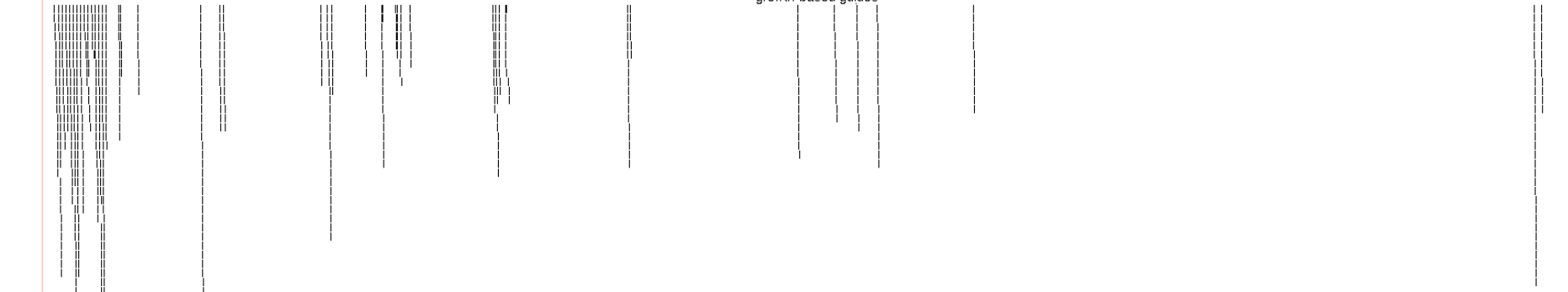
ts





Scale chr2: 38,990,000| 39,000,000| 39,010,000| 39,020,000| 39,030,000| 39,040,000| 39,050,000| 39,060,000| 39,070,000| 39,080,000| 39,090,000| 39,100,000| 39,110,000| 39,120,000| hg38

growth-based guides



## Top 10 ricin genes

#genesymbol	totalSNPs	nClinvarBenignSNPs	nClinvarPathogenicSNPs	nClinvarTotal
NF1	18784	12	68	80
PIK3CA	7111	2	35	37
CDKL5	6792	8	34	42
SMAD4	3631	0	31	31
ACTB	2483	0	26	26
PMM2	1636	2	25	27
SMCHD1	13282	6	22	28
HMBS	2354	0	22	22
TBC1D24	3678	7	20	27
MEN1	3952	5	20	25

					Combo casTLE Effect		casTLE p-value
chr16	8882680	8882681	+	PMM2	8.2	1.00E-06	9.33E-05
chr16	2525147	2525148	+	TBC1D24	4.8	0.000453	0.016388
chr17	29421945	29421946	+	NF1	4.7	1.00E-06	9.33E-05
chr11	64578766	64578767	-	MEN1	4.1	1.00E-06	9.33E-05
chrX	18443703	18443704	+	CDKL5	3.7	0.00362	0.086138
chr7	5603415	5603416	-	ACTB	3.6	7.60E-05	0.004327
chr18	2655737	2655738	+	SMCHD1	2.9	1.00E-06	9.33E-05
chr3	1.79E+08	1.79E+08	+	PIK3CA	2.6	0.000241	0.010178
chr18	48494410	48494411	+	SMAD4	2.5	4.00E-06	0.000339
chr11	1.19E+08	1.19E+08	+	HMBS	2.1	0.00125	0.037083

All guides, i.e. CFD > 0.0

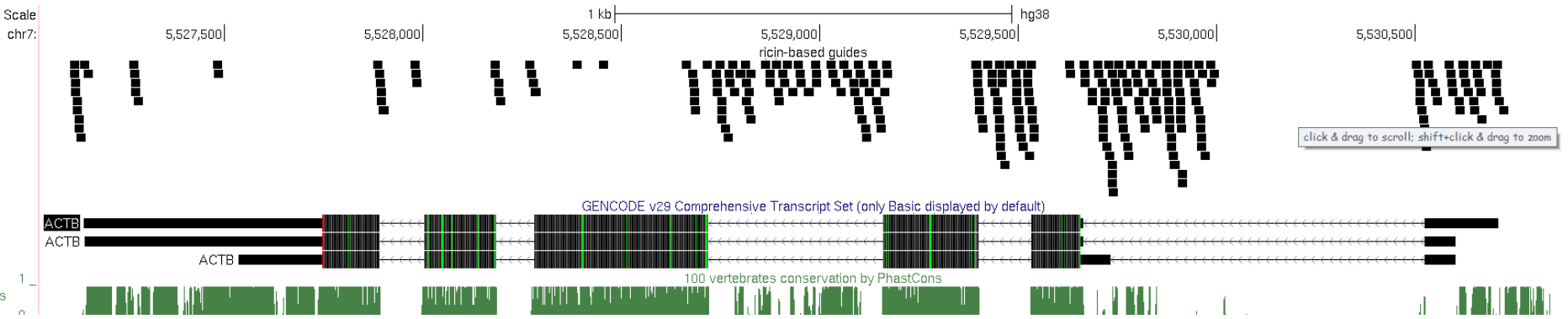
#gene	exons	total_length	total_guides_passing_CFD	fraction_of_bases_covered
ACTB	44	3831	417	0.266249021
CDKL5	43	18167	1590	0.251665107
HMBS	77	5317	817	0.397404551
MEN1	31	4597	942	0.486839243
NF1	102	29548	1830	0.19074049
PIK3CA	30	10430	524	0.14928092
PMM2	41	8152	789	0.263493621
SMAD4	38	13715	1131	0.242726941
SMCHD1	79	14541	967	0.202118149
TBC1D24	29	12642	2018	0.405711122

**Total guides: 11025**

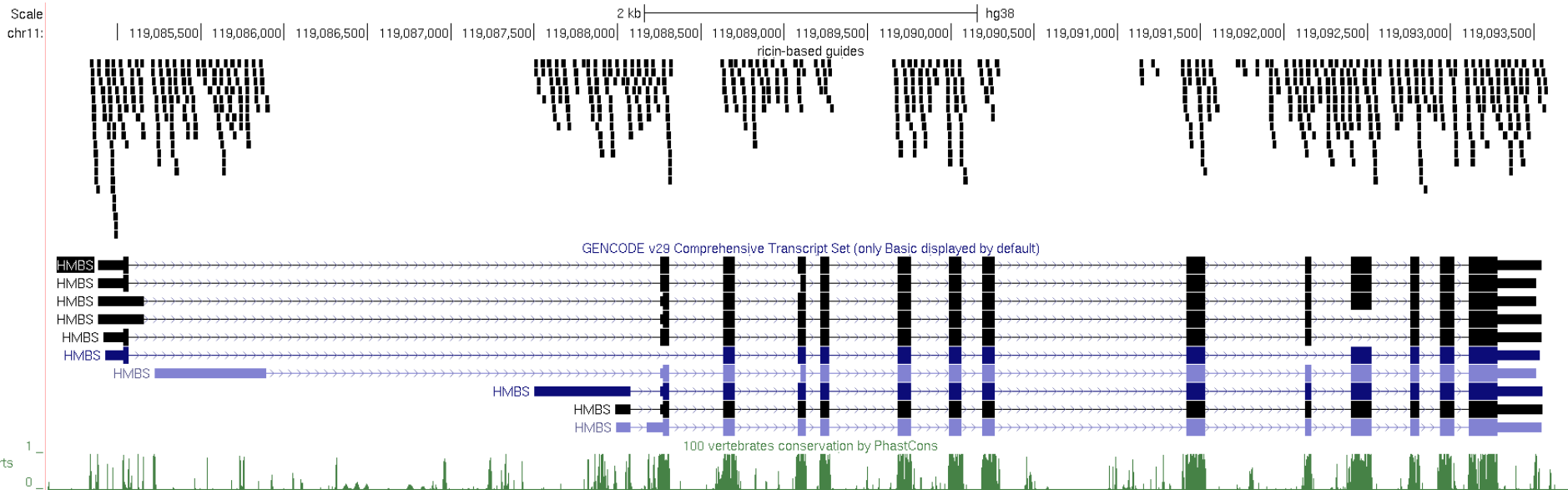
All guides, i.e. CFD > 0.2

<u>#gene</u>	<u>exons</u>	<u>total_length</u>	<u>total_guides_passing_CFD</u>	<u>fraction_of_bases_covered</u>
ACTB	44	3831	267	0.184547116
CDKL5	43	18167	1024	0.173721583
HMBS	77	5317	505	0.277223998
MEN1	31	4597	596	0.350663476
NF1	102	29548	986	0.109313659
PIK3CA	30	10430	290	0.085522531
PMM2	41	8152	521	0.18326791
SMAD4	38	13715	649	0.149325556
SMCHD1	79	14541	557	0.124269307
TBC1D24	29	12642	1046	0.23991457

**Total guides:                      6441**

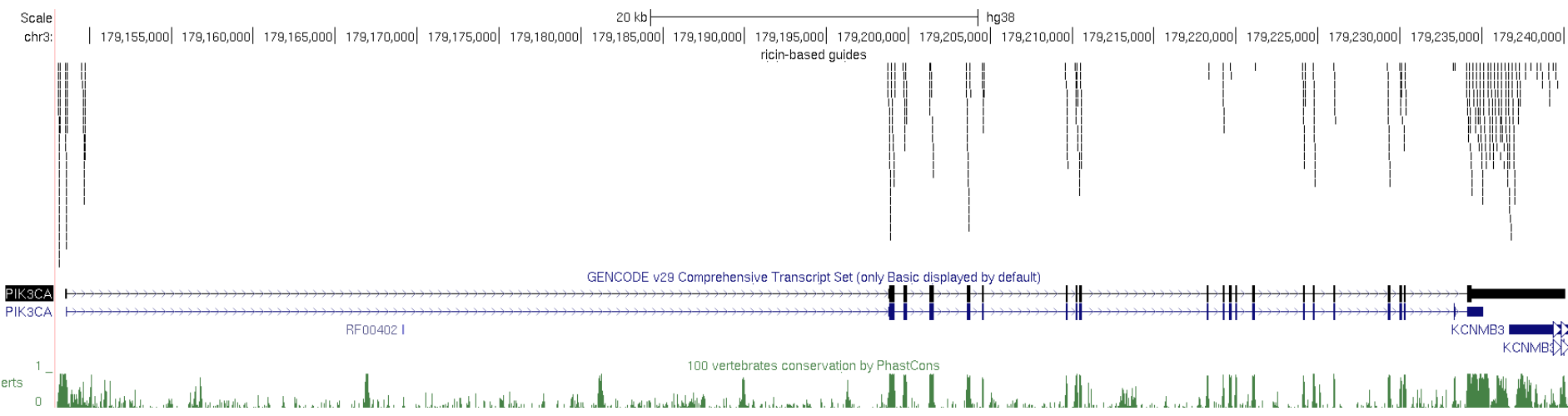


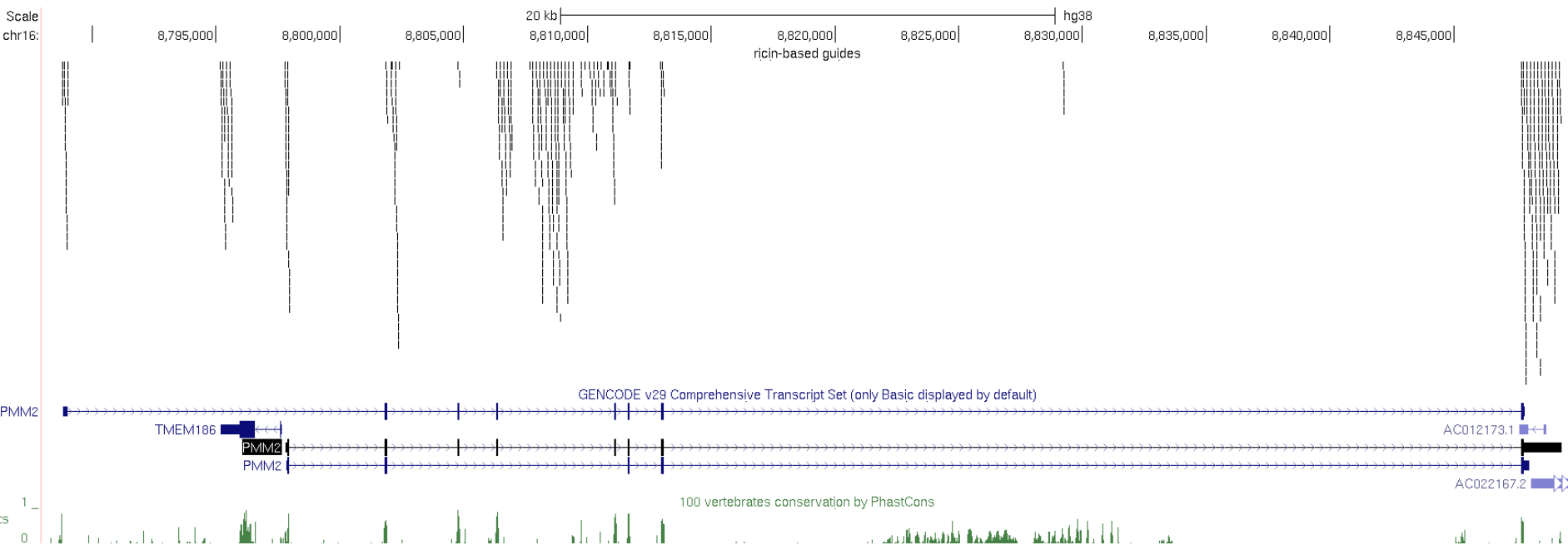












Scale chr18: | 51,035,000 | 51,040,000 | 51,045,000 | 51,050,000 | 51,055,000 | 51,060,000 | 51,065,000 | 51,070,000 | 51,075,000 | 51,080,000 | 51,085,000 | hg38

20 kb |

ricin-based guides

