CADD v1.5

Developmental release

Why a new model?

We were notified that GERP was not properly annotated to the provided set of pre-scored SNV in CADD GRCh38-v1.4. This error was due to how we annotate variants for the whole genome SNV file, i.e. caching values for continuous variant look-ups. As a result, two different scores exist for many SNV based on the pre-scored files versus reannotation from scratch. In order to prevent ambiguity, we decided to release a new model v1.5 for GRCh38.

What's new?

Besides the fixed GERP annotations, the GRCh38-v1.4 release did not use ReMap annotations in the model and we are fixing that in the new release. We further updated all VEP-based annotation to Ensembl release 95 and reduced (unnecessary) precision of several annotations (see Supplement 1 for detail) in order to decrease file size.

Model parameter: The model was trained in the same way as the previous release. The logistic regression used L2 penalty with C = 1 and training was terminated after thirteen L-BFGS iterations; meaning that the two latest models, CADD GRCh38-v1.5 and CADD GRCh37-v1.4, were trained using the same parameters.

Why no GRCh37 model? The updates presented are GRCh38-specific and due to a different file format, the GERP score issue did not apply to GRCh37-v1.4. We therefore decided not to release a new model for GRCh37.

Performance of CADD v1.5 in comparison to v1.4

Please note that the main issue with CADD GRCh38-v1.4 (missing GERP annotations) only affected the pre-scored files that we never used in performance evaluations. Further, including ReMap in training and updating gene/transcript model information has only slightly changed model parameters. Hence, the performance between the models has barely changed.

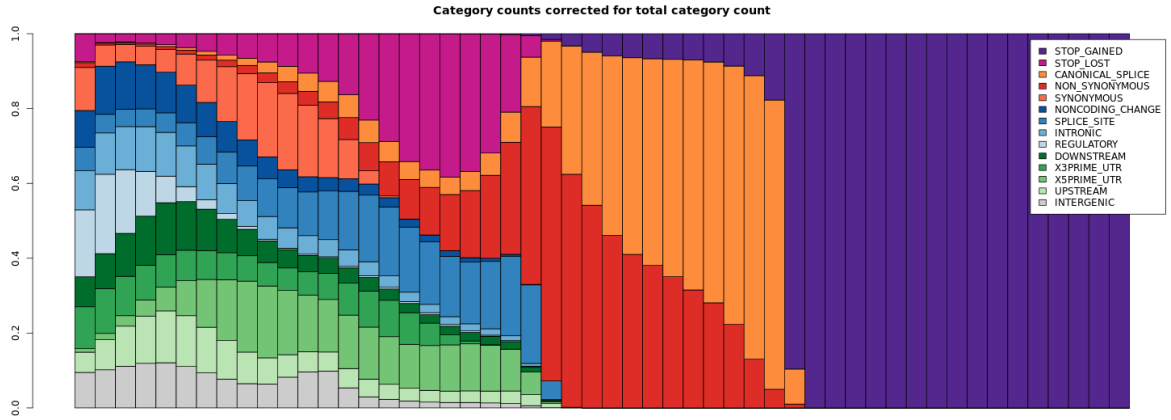
Spearman correlation between the observation frequency of TP53 cancer variants in the IARC database (p53.iarc.fr) and CADD scores changed from 0.474 (GRCh38-v1.4) to 0.473 (GRCh38-v1.5).

Spearman correlation of CADD scores with absolute $\log_2$-fold changes determined from saturation mutagenesis in ALDOB, ECR11 and HBB regulatory sequences (Patwardhan, R.P. et al. Nature Biotechnology 2012, Patwardhan R.P. et al. Nature Biotechnology 2009) changed as follows:

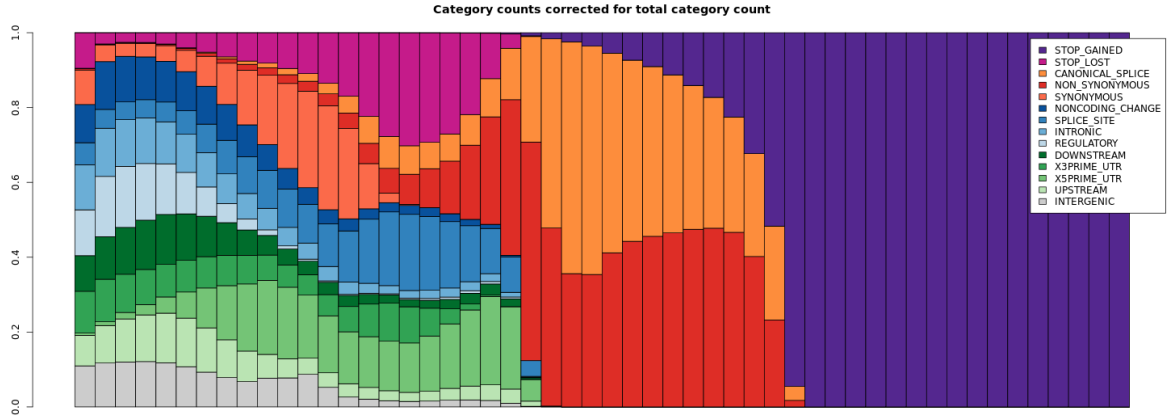
	ALDOB	ECR11	HBB
CADD v1.5 – GRCh38	0.4317	0.0289	0.2416
CADD v1.4 – GRCh38	0.4338	0.0199	0.2385

The performance in distinguishing known pathogenic ClinVar (Landrum, M.J. et al. Nucleic acids Research 2014) variants from frequent variants (allele frequency > 5%) in ExAC (Lek, M., Karczewski K. et al. Nature 2016) has changed from 0.980 (GRCh38-v1.4) to 0.981 (GRCh38-v1.5).

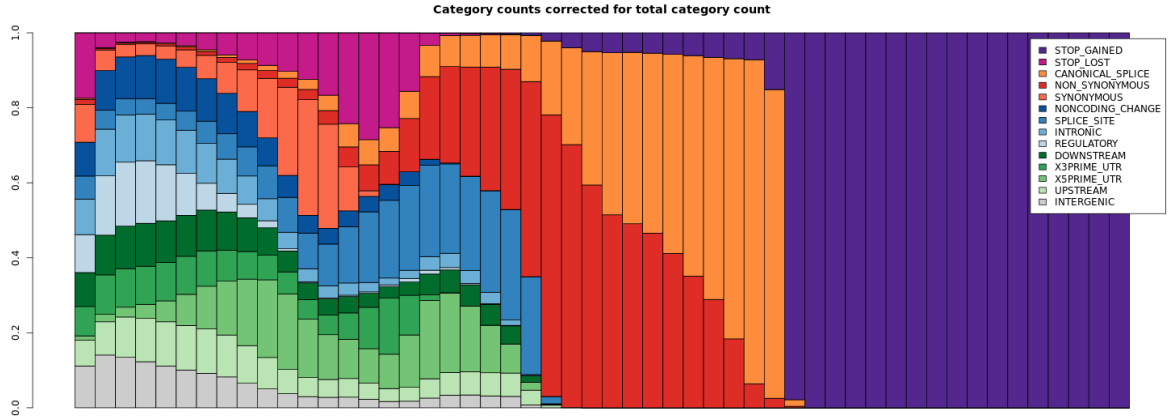
Catgory distribution CADDv1.5-GRCh38



Category distribution CADDv1.4-GRCh38



Catgory distribution CADDv1.4-GRCh37



Supplement 1: Annotations adjusted from CADD GRCh38-v1.4

Annotations based on VEP output, distance2nextTranscript: now based on Ensembl release 95

dbscSNV: reduced to 5 columns and floating point accuracy reduced to 3 digits

GC, CpG, rel…pos: floating point accuracy now 2 digits

GERP++: now annotated to all SNV

Encode expression, nucleosome position, histone modification, open chromatin: floating point accuracy now 2 digits

ReMap: was previously annotated but not used in the model

Supplement 2: Columns in annotation tables of the GRCh38 CADD v1.5 model

	Name	**Type**	**Description**
1	(Chrom)	string	Chromosome
2	(Pos)	integer	Position (1-based)
3	Ref	factor	Reference allele (default: N)
4	Alt	factor	Observed allele (default: N)
5	Type	factor	Event type (SNV, DEL, INS)
6	Length	integer	Number of inserted/deleted bases
7	(AnnoType)	factor	CodingTranscript, Intergenic, MotifFeature, NonCodingTranscript, RegulatoryFeature, Transcript
8	Consequence	factor	VEP consequence, priority selected by potential impact (default: UNKNOWN)
9	(ConsScore)	integer	Custom deleterious score assigned to Consequence
10	(ConsDetail)	string	Trimmed VEP consequence prior to simplification
11	GC	float	Percent GC in a window of +/- 75bp (default: 0.42)
12	CpG	float	Percent CpG in a window of +/- 75bp (default: 0.02)
13	motifECount	integer	Total number of overlapping motifs (default: 0)
14	(motifEName)	string	Name of sequence motif the position overlaps
15	motifEHIPos	bool	Is the position considered highly informative for an overlapping motif by VEP (default: 0)
16	motifEScoreChng	float	VEP score change for the overlapping motif site (default: 0)
17	oAA	factor	Reference amino acid (default: unknown)
18	nAA	factor	Amino acid of observed variant (default: unknown)
19	(GeneID)	string	ENSEMBL GeneID
20	(FeatureID)	string	ENSEMBL feature ID (Transcript ID or regulatory feature ID)
21	(GeneName)	string	GeneName provided in ENSEMBL annotation
22	(CCDS)	string	Consensus Coding Sequence ID
23	(Intron)	string	Intron number/Total number of exons
24	(Exon)	string	Exon number/Total number of exons
25	cDNApos	float	Base position from transcription start (default: 0*)
26	relcDNApos	float	Relative position in transcript (default: 0)
27	CDSpos	float	Base position from coding start (default: 0*)
28	relCDSpos	float	Relative position in coding sequence (default: 0)
29	protPos	float	Amino acid position from coding start (default: 0*)
30	relProtPos	float	Relative position in protein codon (default: 0)

31	Domain	factor	Domain annotation inferred from VEP annotation (ncoils, sigp, lcompl, hmmpanther, ndomain = "other named domain") (default: UD)
32	Dst2Splice	float	Distance to splice site in 20bp; positive: exonic, negative: intronic (default: 0)
33	Dst2SplType	factor	Closest splice site is ACCEPTOR or DONOR (default: unknown)
34	minDistTSS	float	Distance to closest Transcribed Sequence Start (TSS) (default: 5.5)
35	minDistTSE	float	Distance to closest Transcribed Sequence End (TSE) (default: 5.5)
36	SIFTcat	factor	SIFT category of change (default: UD)
37	SIFTval	float	SIFT score (default: 0*)
38	PolyPhenCat	factor	PolyPhen category of change (default: UD)
39	PolyPhenVal	float	PolyPhen score (default: 0*)
40	priPhCons	float	Primate PhastCons conservation score (excl. human) (default: 0.0)
41	mamPhCons	float	Mammalian PhastCons conservation score (excl. human) (default: 0.0)
42	verPhCons	float	Vertebrate PhastCons conservation score (excl. human) (default: 0.0)
43	priPhyloP	float	Primate PhyloP score (excl. human) (default: -0.029)
44	mamPhyloP	float	Mammalian PhyloP score (excl. human) (default: -0.005)
45	verPhyloP	float	Vertebrate PhyloP score (excl. human) (default: 0.042)
46	bStatistic	integer	Background selection score (default: 800)
47	targetScan	integer	targetscan (default: 0*)
48	mirSVR-Score	float	mirSVR-Score (default: 0*)
49	mirSVR-E	float	mirSVR-E (default: 0)
50	mirSVR-Aln	integer	mirSVR-Aln (default: 0)
51	cHmm_E1	float	Number of 48 cell types in chromHMM state E1_poised (default: 1.92*)
52	cHmm_E2	float	Number of 48 cell types in chromHMM state E2_repressed (default: 1.92)
53	cHmm_E3	float	Number of 48 cell types in chromHMM state E3_dead (default: 1.92)
54	cHmm_E4	float	Number of 48 cell types in chromHMM state E4_dead (default: 1.92)
55	cHmm_E5	float	Number of 48 cell types in chromHMM state E5_repressed (default: 1.92)
56	cHmm_E6	float	Number of 48 cell types in chromHMM state E6_repressed (default: 1.92)
57	cHmm_E7	float	Number of 48 cell types in chromHMM state E7_weak (default: 1.92)
58	cHmm_E8	float	Number of 48 cell types in chromHMM state E8_gene (default: 1.92)
59	cHmm_E9	float	Number of 48 cell types in chromHMM state E9_gene (default: 1.92)
60	cHmm_E10	float	Number of 48 cell types in chromHMM state E10_gene (default: 1.92)
61	cHmm_E11	float	Number of 48 cell types in chromHMM state E11_gene (default: 1.92)
62	cHmm_E12	float	Number of 48 cell types in chromHMM state E12_distal (default: 1.92)
63	cHmm_E13	float	Number of 48 cell types in chromHMM state E13_distal (default: 1.92)
64	cHmm_E14	float	Number of 48 cell types in chromHMM state E14_distal (default: 1.92)

65	cHmm_E15	float	Number of 48 cell types in chromHMM state E15_weak (default: 1.92)
66	cHmm_E16	float	Number of 48 cell types in chromHMM state E16_tss (default: 1.92)
67	cHmm_E17	float	Number of 48 cell types in chromHMM state E17_proximal (default: 1.92)
68	cHmm_E18	float	Number of 48 cell types in chromHMM state E18_proximal (default: 1.92)
69	cHmm_E19	float	Number of 48 cell types in chromHMM state E19_tss (default: 1.92)
70	cHmm_E20	float	Number of 48 cell types in chromHMM state E20_poised (default: 1.92)
71	cHmm_E21	float	Number of 48 cell types in chromHMM state E21_dead (default: 1.92)
72	cHmm_E22	float	Number of 48 cell types in chromHMM state E22_repressed (default: 1.92)
73	cHmm_E23	float	Number of 48 cell types in chromHMM state E23_weak (default: 1.92)
74	cHmm_E24	float	Number of 48 cell types in chromHMM state E24_distal (default: 1.92)
75	cHmm_E25	float	Number of 48 cell types in chromHMM state E25_distal (default: 1.92)
76	GerpRS	float	Gerp element score (default: 0)
77	GerpRSpval	float	Gerp element p-Value (default: 0)
78	GerpN	float	Neutral evolution score defined by GERP++ (default: 3.0)
79	GerpS	float	Rejected Substitution score defined by GERP++ (default: -0.2)
80	tOverlapMotifs	float	Number of overlapping predicted TF motifs
81	motifDist	float	Reference minus alternate allele difference in nucleotide frequency within an predicted overlapping motif (default: 0)
82	EncodeH3K4me1-sum	float	Sum of Encode H3K4me1 levels (from 13 cell lines) (default: 0.76)
83	EncodeH3K4me1-max	float	Maximum Encode H3K4me1 level (from 13 cell lines) (default: 0.37)
84	EncodeH3K4me2-sum	float	Sum of Encode H3K4me2 levels (from 14 cell lines) (default: 0.73)
85	EncodeH3K4me2-max	float	Maximum Encode H3K4me2 level (from 14 cell lines) (default: 0.37)
86	EncodeH3K4me3-sum	float	Sum of Encode H3K4me3 levels (from 14 cell lines) (default: 0.81)
87	EncodeH3K4me3-max	float	Maximum Encode H3K4me3 level (from 14 cell lines) (default: 0.38)
88	EncodeH3K9ac-sum	float	Sum of Encode H3K9ac levels (from 13 cell lines) (default: 0.82)
89	EncodeH3K9ac-max	float	Maximum Encode H3K9ac level (from 13 cell lines) (default: 0.41)
90	EncodeH3K9me3-sum	float	Sum of Encode H3K9me3 levels (from 14 cell lines) (default: 0.81)
91	EncodeH3K9me3-max	float	Maximum Encode H3K9me3 level (from 14 cell lines) (default: 0.38)
92	EncodeH3K27ac-sum	float	Sum of Encode H3K27ac levels (from 14 cell lines) (default: 0.74)
93	EncodeH3K27ac-max	float	Maximum Encode H3K27ac level (from 14 cell lines) (default: 0.36)
94	EncodeH3K27me3-sum	float	Sum of Encode H3K27me3 levels (from 14 cell lines) (default: 0.93)
95	EncodeH3K27me3-max	float	Maximum Encode H3K27me3 level (from 14 cell lines) (default: 0.47)
96	EncodeH3K36me3-sum	float	Sum of Encode H3K36me3 levels (from 10 cell lines) (default: 0.71)
97	EncodeH3K36me3-max	float	Maximum Encode H3K36me3 level (from 10 cell lines) (default: 0.39)

98	EncodeH3K79me2-sum	float	Sum of Encode H3K79me2 levels (from 13 cell lines) (default: 0.64)
99	EncodeH3K79me2-max	float	Maximum Encode H3K79me2 level (from 13 cell lines) (default: 0.34)
100	EncodeH4K20me1-sum	float	Sum of Encode H4K20me1 levels (from 11 cell lines) (default: 0.88)
101	EncodeH4K20me1-max	float	Maximum Encode H4K20me1 level (from 11 cell lines) (default: 0.47)
102	EncodeH2AFZ-sum	float	Sum of Encode H2AFZ levels (from 13 cell lines) (default: 0.9)
103	EncodeH2AFZ-max	float	Maximum Encode H2AFZ level (from 13 cell lines) (default: 0.42)
104	EncodeDNase-sum	float	Sum of Encode DNase-seq levels (from 12 cell lines) (default: 0.0)
105	EncodeDNase-max	float	Maximum Encode DNase-seq level (from 12 cell lines) (default: 0.0)
106	EncodetotalRNA-sum	float	Sum of Encode totalRNA-seq levels (from 10 cell lines always minus and plus strand) (default: 0.0)
107	EncodetotalRNA-max	float	Maximum Encode totalRNA-seq level (from 10 cell lines, minus and plus strand separately) (default: 0.0)
108	Grantham	float	Grantham score: oAA,nAA (default: 0*)
109	Dist2Mutation	float	Distance between the closest BRAVO SNV up and downstream (position itself excluded) (default: 0*)
110	Freq100bp	integer	Number of frequent (MAF > 0.05) BRAVO SNV in 100 bp window nearby (default: 0)
111	Rare100bp	integer	Number of rare (MAF < 0.05) BRAVO SNV in 100 bp window nearby (default: 0)
112	Sngl100bp	integer	Number of single occurrence BRAVO SNV in 100 bp window nearby (default: 0)
113	Freq1000bp	integer	Number of frequent (MAF > 0.05) BRAVO SNV in 1000 bp window nearby (default: 0)
114	Rare1000bp	integer	Number of rare (MAF < 0.05) BRAVO SNV in 1000 bp window nearby (default: 0)
115	Sngl1000bp	integer	Number of single occurrence BRAVO SNV in 1000 bp window nearby (default: 0)
116	Freq10000bp	integer	Number of frequent (MAF > 0.05) BRAVO SNV in 10000 bp window nearby (default: 0)
117	Rare10000bp	integer	Number of rare (MAF < 0.05) BRAVO SNV in 10000 bp window nearby (default: 0)
118	Sngl10000bp	integer	Number of single occurrence BRAVO SNV in 10000 bp window nearby (default: 0)
119	EnsembleRegulatory-Feature	factor	Matches in the Ensemble Regulatory Built (similar to annotype) (default: NA)
120	dbscSNV-ada_score	float	Adaboost classifier score from dbscSNV (default: 0*)
121	dbscSNV-rf_score	float	Random forest classifier score from dbscSNV (default: 0*)
122	RemapOverlapTF	integer	Remap number of different transcription factors binding (default: -0.5)
123	RemapOverlapCL	integer	Remap number of different transcription factor - cell line combinations binding (default: -0.5)
124	RawScore	float	Raw score from the model
125	PHRED	float	CADD PHRED Score

* A Boolean indicator variable was created in order to handle undefined values. Note that often indicators represent more than one annotation. They are created for only (the first) one if the covered genomic regions are identical.