

# Structural, functional and evolutionary analysis of calsequestrin2

## 钙结合蛋白calsequestrin2的结构、功能及 进化分析

Members of G05: 童泽鑫, 马昕蕾, 刘艺, 姜智胜

Reporter: 童泽鑫

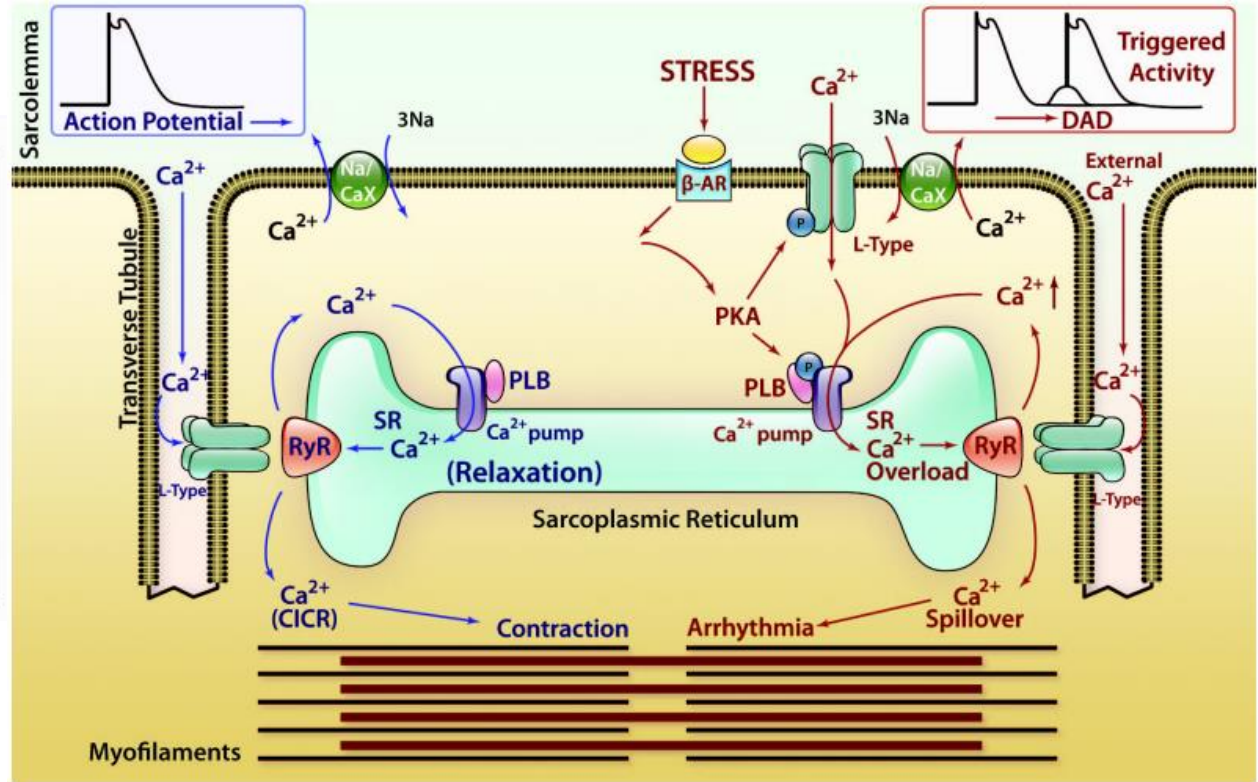
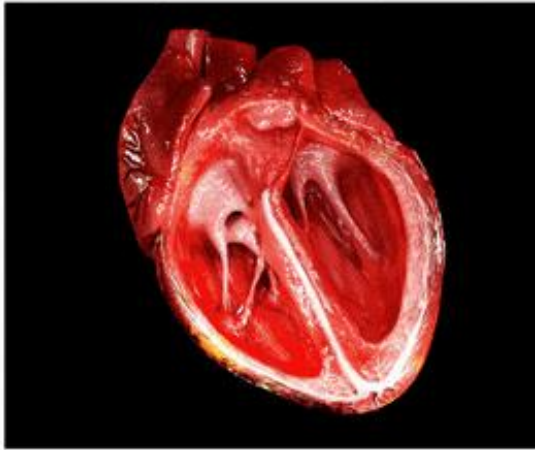
January 12, 2019

# Content

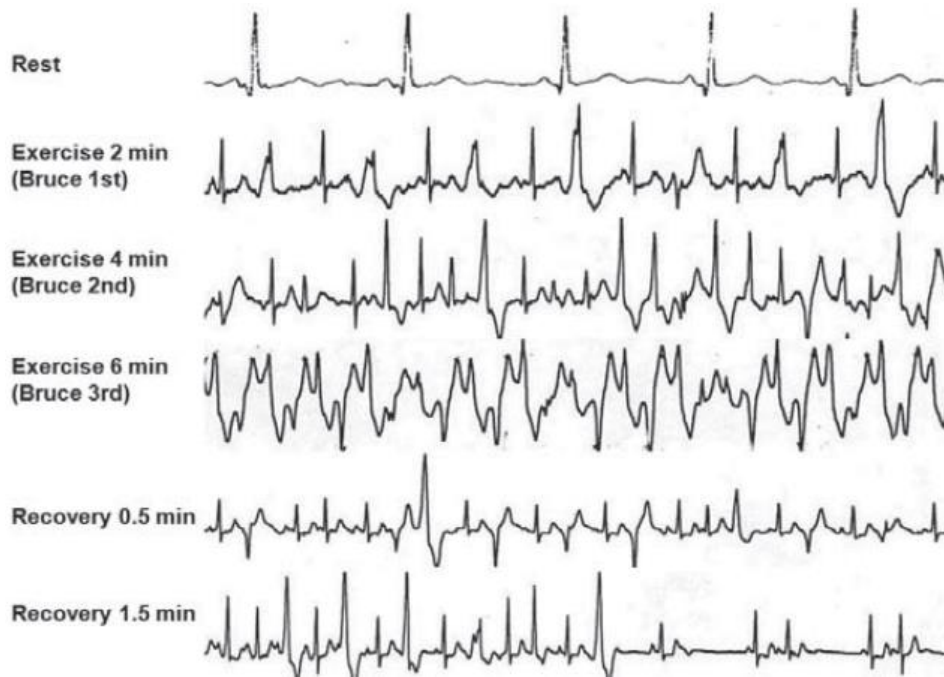
- 背景
- 序列分析
- 系统发生树构建
- 结构分析
- 功能分析
- 展望（疾病治疗）

# CICR SOICR and Triggered Arrhythmia

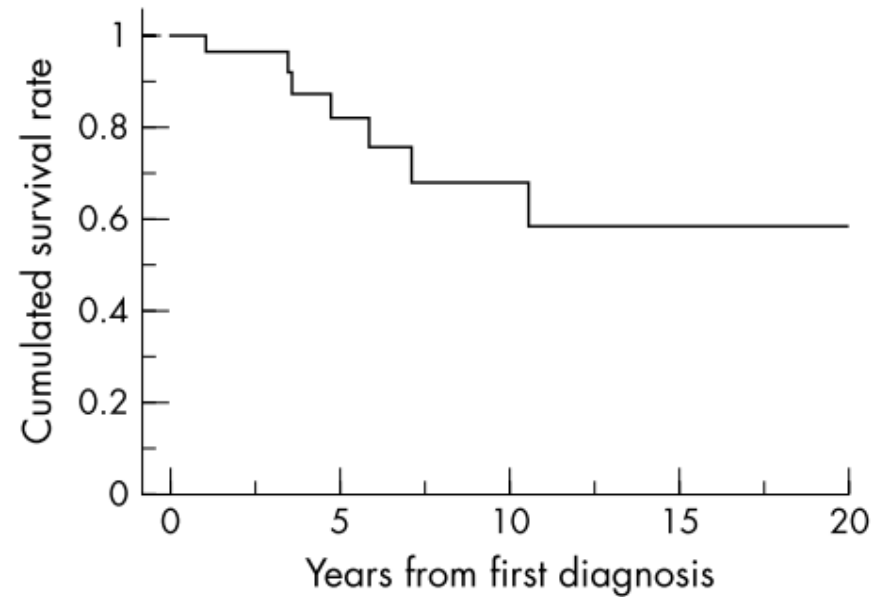
CARDIAC CYCLE



# Catecholaminergic Polymorphic Ventricular Tachycardia

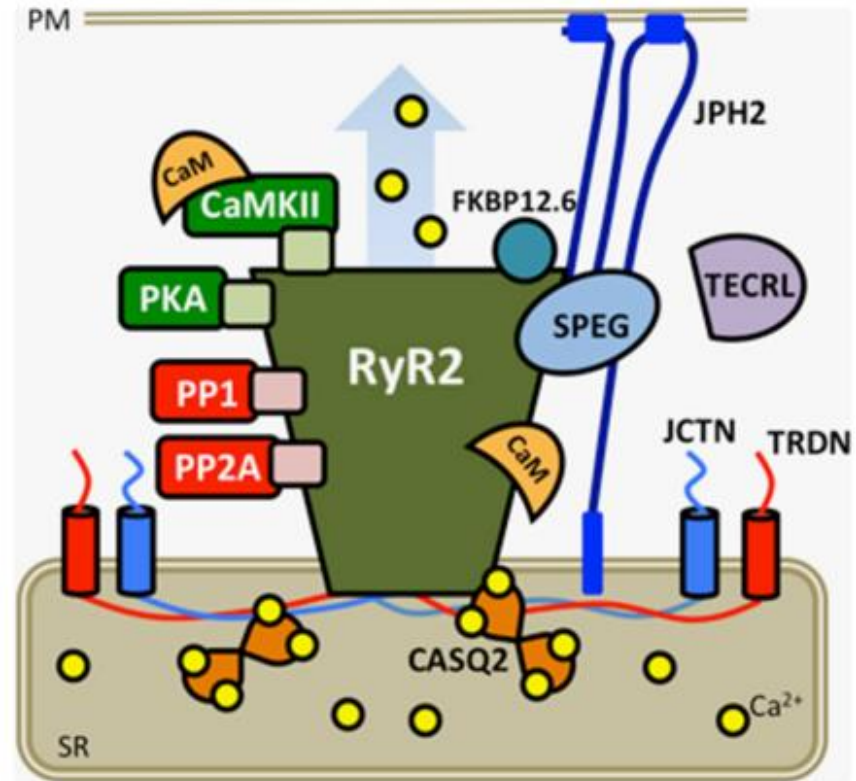
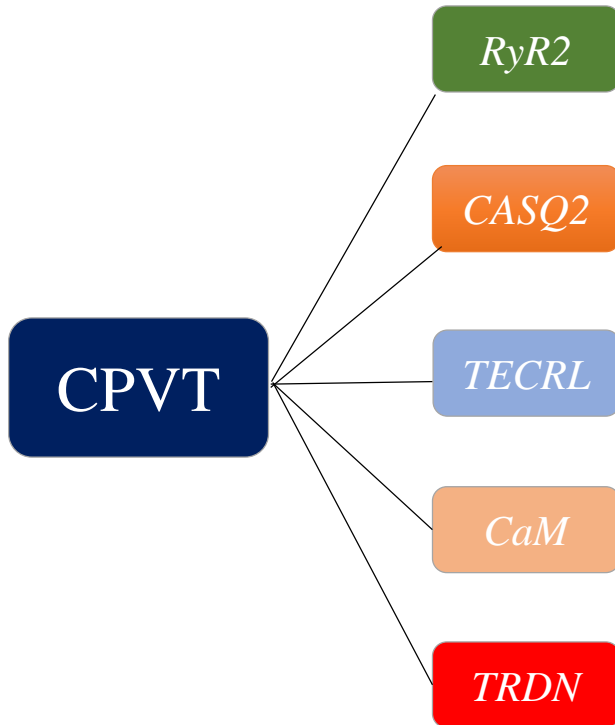


ECG pattern of a CPVT patient

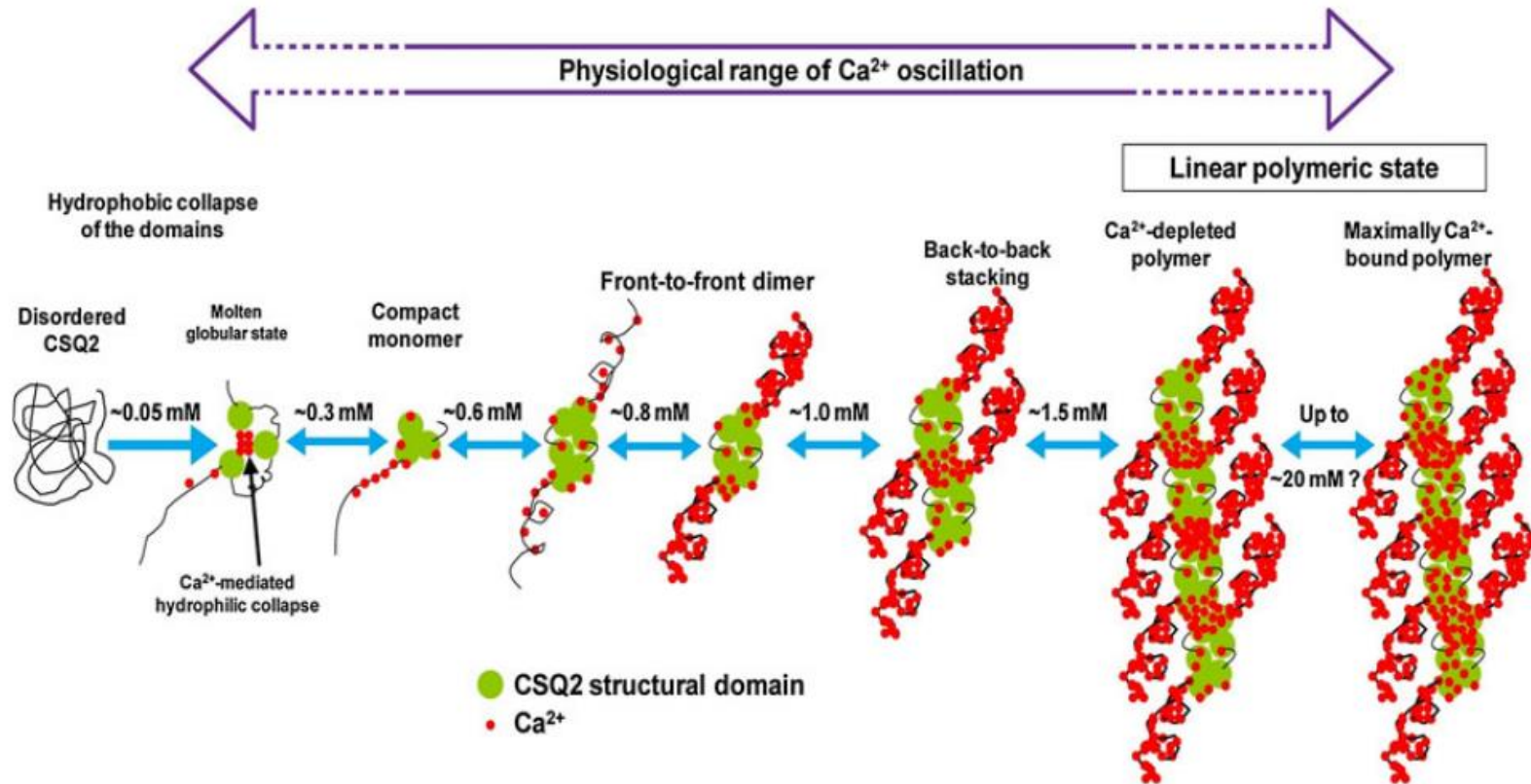


Cumulative survival rates

# Genes Related to CPVT

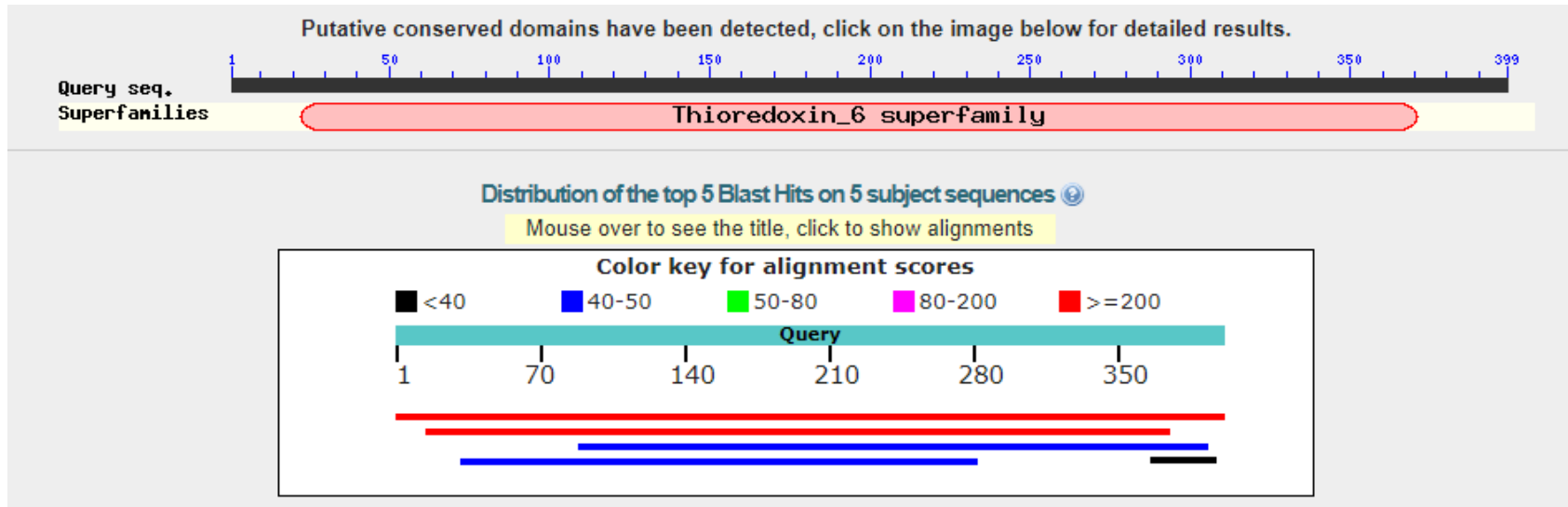


# Polymerization of CASQ2



# Sequence analysis

# Protein blast for similar sequences



## Sequences producing significant alignments:

Select: [All](#) [None](#) Selected:0

[Alignments](#) [Download](#) [GenPept](#) [Graphics](#) [Distance tree of results](#) [Multiple alignment](#)

	Description	Max score	Total score	Query cover	E value	Ident	Accession
<input type="checkbox"/>	<a href="#">RecName: Full=Calsequestrin-2; AltName: Full=Calsequestrin, cardiac muscle isoform; Flags: Precursor</a>	796	796	100%	0.0	100%	<a href="#">Q14958.2</a>
<input checked="" type="checkbox"/>	<a href="#">RecName: Full=Calsequestrin-1; AltName: Full=Calmitine; AltName: Full=Calsequestrin, skeletal muscle isoform; Flags: Precursor</a>	520	520	89%	0.0	68%	<a href="#">P31415.3</a>
<input type="checkbox"/>	<a href="#">RecName: Full=Endoplasmic reticulum resident protein 44; Short=ER protein 44; Short=ERp44; AltName: Full=Thioredoxin domain-containing protein 4; Flags: Precursor</a>	46.6	46.6	75%	1e-05	21%	<a href="#">Q9BS26.1</a>
<input type="checkbox"/>	<a href="#">RecName: Full=Protein disulfide-isomerase; Short=PDI; AltName: Full=Cellular thyroid hormone-binding protein; AltName: Full=Proyl 4-hydroxylase subunit beta; AltName: Full=</a>	41.2	41.2	62%	7e-04	23%	<a href="#">P07237.3</a>
<input type="checkbox"/>	<a href="#">RecName: Full=E3 ubiquitin-protein ligase UBR5; AltName: Full=E3 ubiquitin-protein ligase, HECT domain-containing 1; AltName: Full=HECT-type E3 ubiquitin transferase UBR</a>	28.9	28.9	8%	6.6	38%	<a href="#">Q95071.2</a>



# Sequence alignment

G3RLH3	G3RLH3_GORGO	1	MKRTHLFI VGIYFLSSCRAEGLNFPPTYDGKDRVSVLSEKNFKQVLKKYDLLCLYYHEPV	60
Q5RAN9	CASQ2_PONAB	1	MKRTHLFI VGIYFLSSCRAEGLNFPPTYDGKDRVSVLSEKNFKQVLKKYDLLCLYYHEPV	60
H2PZR3	H2PZR3_PANTR	1	MKRTHLFI VGIYFLSSCRAEGLNFPPTYDGKDRVSVLSEKNFKQVLKKYDLLCLYYHEPV	60
A0A2K6B9U7	A0A2K6B9U7_MACNE	1	MKRTHLFI VGIYFLSSCRAEGLNFPPTYDGKDRVSVLSEKNFKQVLKKYDLLCLYYHEPV	60
A0A096MW08	A0A096MW08_PAPAN	1	MKRTHLFI VGIYFLSSCRAEGLNFPPTYDGKDRVSVLSEKNFKQVLKKYDLLCLYYHEPV	60
F7EQW4	F7EQW4_MACMU	1	MKRTHLFI VGIYFLSSCRAEGLNFPPTYDGKDRVSVLSEKNFKQVLKKYDLLCLYYHEPV	60
O14958	CASQ2_HUMAN	1	MKRTHLFI VGIYFLSSCRAEGLNFPPTYDGKDRVSVLSEKNFKQVLKKYDLLCLYYHEPV	60
*****;*.*****				
G3RLH3	G3RLH3_GORGO	61	SSDKVAQKQFQLKEIVLELVAQVLEHKAIGFVMVDAKKEAKLAKKLGFDDEEGSLYILKGD	120
Q5RAN9	CASQ2_PONAB	61	SSDKVAQKQFQLKEIVLELVAQVLEHKAIGFVMVDAKKEAKLAKKLGFDDEEGSLYILKGD	120
H2PZR3	H2PZR3_PANTR	61	SSDKVAQKQFQLKEIVLELVAQVLEHKAIGFVMVDAKKEAKLAKKLGFDDEEGSLYILKGD	120
A0A2K6B9U7	A0A2K6B9U7_MACNE	61	SSDKVAQKQFQLKEIVLELVAQVLEHKAIGFVMVDAKKEAKLAKKLGFDDEEGSLYILKGD	120
A0A096MW08	A0A096MW08_PAPAN	61	SSDKVAQKQFQLKEIVLELVAQVLEHKAIGFVMVDAKKEAKLAKKLGFDDEEGSLYILKGD	120
F7EQW4	F7EQW4_MACMU	61	SSDKVAQKQFQLKEIVLELVAQVLEHKAIGFVMVDAKKEAKLAKKLGFDDEEGSLYILKGD	120
O14958	CASQ2_HUMAN	61	SSDKVTKQKQFQLKEIVLELVAQVLEHKAIGFVMVDAKKEAKLAKKLGFDDEEGSLYILKGD	120
*****;*****				
G3RLH3	G3RLH3_GORGO	121	RTIEFDGEFAADVLVEFLLDLIEDPVEI ISSKLEVQAFERIEDYIKLIGFFKSEDSYYK	180
Q5RAN9	CASQ2_PONAB	121	RTIEFDGEFAADVLVEFLLDLIEDPVEI ISSKLEVQAFERIEDYIKLIGFFKSGDSEYYK	180
H2PZR3	H2PZR3_PANTR	121	RTIEFDGEFAADVLVEFLLDLIEDPVEI ISSKLEVQAFERIEDYIKLIGFFKSEDSYYK	180
A0A2K6B9U7	A0A2K6B9U7_MACNE	121	RTIEFDGEFAADVLVEFLLDLIEDPVEI ISSKLEVQAFERIEDYIKLIGFFKSEDSYYK	180
A0A096MW08	A0A096MW08_PAPAN	121	RTIEFDGEFAADVLVEFLLDLIEDPVEI ISSKLEVQAFERIEDYIKLIGFFKSEDSYYK	180
F7EQW4	F7EQW4_MACMU	121	RTIEFDGEFAADVLVEFLLDLIEDPVEI ISSKLEVQAFERIEDYIKLIGFFKSEDSYYK	180
O14958	CASQ2_HUMAN	121	RTIEFDGEFAADVLVEFLLDLIEDPVEI ISSKLEVQAFERIEDYIKLIGFFKSEDSYYK	180
*****;*****				
G3RLH3	G3RLH3_GORGO	181	AFEEAAEHFPQYIKFFATFDKGVAKKLSLKMNEVDFYEPFMDEPIAIPNKPYTEEEIVF	240
Q5RAN9	CASQ2_PONAB	181	AFEEAAEHFPQYIKFFATFDKGVAKKLSLKMNEVDFYEPFMDEPIAIPNKPYTEEEIVF	240
H2PZR3	H2PZR3_PANTR	181	AFEEAAEHFPQYIKFFATFDKGVAKKLSLKMNEVDFYEPFMDEPIAIPNKPYTEEEIVF	240
A0A2K6B9U7	A0A2K6B9U7_MACNE	181	AFEEAAEHFPQYIKFFATFDKGVAKKLSLKMNEVDFYEPFMDEPIAIPNKPYTEEEIVF	240
A0A096MW08	A0A096MW08_PAPAN	181	AFEEAAEHFPQYIKFFATFDKGVAKKLSLKMNEVDFYEPFMDEPIAIPNKPYTEEEIVF	240
F7EQW4	F7EQW4_MACMU	181	AFEEAAEHFPQYIKFFATFDKGVAKKLSLKMNEVDFYEPFMDEPIAIPNKPYTEEEIVF	240
O14958	CASQ2_HUMAN	181	AFEEAAEHFPQYIKFFATFDKGVAKKLSLKMNEVDFYEPFMDEPIAIPNKPYTEEEIVF	240
*****;***				
G3RLH3	G3RLH3_GORGO	241	VKEHQRPTRLRRLPEEMFETWEDDLNGIHIVAFAEKSDPDGYEFLEILKQVARDNTDNDP	300
Q5RAN9	CASQ2_PONAB	241	VKEHQRPTRLRRLPEEMFETWEDDLNGIHIVAFAEKSDPDGYEFLEILKQVARDNTDNDP	300
H2PZR3	H2PZR3_PANTR	241	VKEHQRPTRLRRLPEEMFETWEDDLNGIHIVAFAEKSDPDGYEFLEILKQVARDNTDNDP	300
A0A2K6B9U7	A0A2K6B9U7_MACNE	241	VKEHQRPTRLRRLPEEMFETWEDDLNGIHIVAFAEKSDPDGYEFLEILKQVARDNTDNDP	300
A0A096MW08	A0A096MW08_PAPAN	241	VKEHQRPTRLRRLPEEMFETWEDDLNGIHIVAFAEKSDPDGYEFLEILKQVARDNTDNDP	300
F7EQW4	F7EQW4_MACMU	241	VKEHQRPTRLRRLPEEMFETWEDDLNGIHIVAFAEKSDPDGYEFLEILKQVARDNTDNDP	300
O14958	CASQ2_HUMAN	241	VKEHQRPTRLRRLPEEMFETWEDDLNGIHIVAFAEKSDPDGYEFLEILKQVARDNTDNDP	300
***;*****				
G3RLH3	G3RLH3_GORGO	301	LSILWIDPDDFPLLVAWYKFTFKIDLFRPQIGVVNVDADSVWMEIPDDDDLPAAELED	360
Q5RAN9	CASQ2_PONAB	301	LSILWIDPDDFPLLVAWYKFTFKIDLFRPQIGVVNVDADSVWMEIPDDDDLPAAELED	360
H2PZR3	H2PZR3_PANTR	301	LSILWIDPDDFPLLVAWYKFTFKIDLFRPQIGVVNVDADSVWMEIPDDDDLPAAELED	360
A0A2K6B9U7	A0A2K6B9U7_MACNE	301	LSILWIDPDDFPLLVAWYKFTFKIDLFRPQIGVVNVDADSVWMEIPDDDDLPAAELED	360
A0A096MW08	A0A096MW08_PAPAN	301	LSILWIDPDDFPLLVAWYKFTFKIDLFRPQIGVVNVDADSVWMEIPDDDDLPAAELED	360
F7EQW4	F7EQW4_MACMU	301	LSILWIDPDDFPLLVAWYKFTFKIDLFRPQIGVVNVDADSVWMEIPDDDDLPAAELED	360
O14958	CASQ2_HUMAN	301	LSILWIDPDDFPLLVAWYKFTFKIDLFRPQIGVVNVDADSVWMEIPDDDDLPAAELED	360
*****				
G3RLH3	G3RLH3_GORGO	361	WIEDVLSGKINTEDEDDDDDDNSDEE-DNDDSDDDDE-	399
Q5RAN9	CASQ2_PONAB	361	WIEDVLSGKINTEDEDDDDDDNSDEE-DNDDSDDDDE-	400
H2PZR3	H2PZR3_PANTR	361	WIEDVLSGKINTEDEDDDDDDNSDEE-DNDDSDDDDE-	399
A0A2K6B9U7	A0A2K6B9U7_MACNE	361	WIEDVLSGKINTEDEDDDDDDNSDEE-DNDDSDDDDE-	400
A0A096MW08	A0A096MW08_PAPAN	361	WIEDVLSGKINTEDEDDDDDDNSDEE-DNDDSDDDDE-	400
F7EQW4	F7EQW4_MACMU	361	WIEDVLSGKINTEDEDDDDDDNSDEE-DNDDSDDDDE-	400
O14958	CASQ2_HUMAN	361	WIEDVLSGKINTEDEDDDDDDNSDEE-DNDDSDDDDE-	399
*****;*****;...::*****;				

# Sequence alignment

	LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
Gorilla	399	2077.0	397/399 (99.5%)	398/399 (99.7%)	0/399 ( 0.0%)
Pongo abelii	400	2059.0	392/400 (98.0%)	396/400 (99.0%)	1/400 ( 0.2%)
Macaca nemestrina	400	2053.0	391/400 (97.8%)	397/400 (99.2%)	1/400 ( 0.2%)
Papio anubis	400	2053.0	391/400 (97.8%)	397/400 (99.2%)	1/400 ( 0.2%)
Macaca mulata	400	2053.0	391/400 (97.8%)	397/400 (99.2%)	1/400 ( 0.2%)
Chimpanzee	400	2058.0	397/400 (99.2%)	397/400 (99.2%)	2/400 ( 0.5%)

## Basic Options

\* Gap opening penalty (10.0 for any sequence):



\* Gap extension penalty (0.5 for any sequence):



# Sequence alignment

## Rat

LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
412	1913.0	365/412 (88.6%)	383/412 (93.0%)	14/412 ( 3.4%)

CASQ2_HUMAN	1	MKRTHLFI	VGIYFLSS	CR	AEEGLN	FPTYD	GKDR	RVVSL	SEKN	FQVL	KKYD	50	
CASQ2_RAT	1	MKRIYLLV	GVLYLLS	FR	AEEGLN	FPTYD	GKDR	RVVSL	SEKN	LKQV	LKRYD	50	
CASQ2_HUMAN	51	LLCLYYHE	PVSSDK	VT	QKQF	QLKE	IV	LELVA	QVLE	HKAI	GFVM	DAKKEA	100
CASQ2_RAT	51	LLCLYYHE	PVSSDK	V	QKQF	QLKE	IV	LELVA	QVLE	HKNI	GFVM	DRKEA	100
CASQ2_HUMAN	101	KLAKKLG	FDEEGS	LYIL	KGDR	TI	EF	DGEF	AA	DL	IEDP	VEIIS	150
CASQ2_RAT	101	KLAKR	LGFSE	EGS	LYV	KGGR	T	IE	FD	GE	FA	ADVLE	FL
CASQ2_HUMAN	151	SKLEVQ	A	F	E	R	I	E	D	Y	I	K	L
CASQ2_RAT	151	NKLEVQ	A	F	E	R	I	E	D	Q	I	K	L
CASQ2_HUMAN	201	KGVA	AK	LS	L	K	M	N	E	V	D	F	Y
CASQ2_RAT	201	KGVA	AK	LS	L	K	M	N	E	V	D	F	Y
CASQ2_HUMAN	251	RLR	P	E	M	F	E	T	W	E	D	L	N
CASQ2_RAT	251	PLR	P	E	D	M	F	E	T	W	E	D	L
CASQ2_HUMAN	301	LS	I	L	W	I	D	P	D	F	L	L	V
CASQ2_RAT	301	LS	I	L	W	I	D	P	D	F	L	L	V
CASQ2_HUMAN	351	DL	P	T	A	E	E	L	E	D	W	I	E
CASQ2_RAT	351	DL	P	T	A	E	E	L	E	D	W	I	E
CASQ2_HUMAN	388	ED	N	D	S	D	D	D	D	D	D	D	E
CASQ2_RAT	400	ED	N	D	S	D	D	D	D	D	D	D	D

## Mouse

LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
413	1894.0	359/413 (86.9%)	384/413 (93.0%)	14/413 ( 3.4%)

CASQ2_HUMAN	1	MKRTHLFI	VGIYFLSS	CR	AEEGLN	FPTYD	GKDR	RVVSL	SEKN	FQVL	KKYD	50	
CASQ2_MOUSE	1	MKRIYLLM	GVYLLS	FR	AEEGLN	FPTYD	GKDR	RVVSL	SEKN	LKQV	LKRYD	50	
CASQ2_HUMAN	51	LLCLYYHE	PVSSDK	VT	QKQF	QLKE	IV	LELVA	QVLE	HKAI	GFVM	DAKKEA	100
CASQ2_MOUSE	51	LLCLYYHE	PVSSDK	V	QKQF	QLKE	IV	LELVA	QVLE	HKNI	GFVM	DRKEA	100
CASQ2_HUMAN	101	KLAKKLG	FDEEGS	LYIL	KGDR	TI	EF	DGEF	AA	DL	IEDP	VEIIS	150
CASQ2_MOUSE	101	KLAKR	LGFSE	EGS	LYV	KGDR	T	IE	FD	GE	FA	ADVLE	FL
CASQ2_HUMAN	151	SKLEVQ	A	F	E	R	I	E	D	Y	I	K	L
CASQ2_MOUSE	151	NKLEVQ	A	F	E	R	I	E	D	Q	I	K	L
CASQ2_HUMAN	201	KGVA	AK	LS	L	K	M	N	E	V	D	F	Y
CASQ2_MOUSE	201	KAVA	AK	LS	L	K	M	N	E	V	D	F	Y
CASQ2_HUMAN	251	RLR	P	E	M	F	E	T	W	E	D	L	N
CASQ2_MOUSE	251	RVA	AK	LS	L	K	M	N	E	V	D	F	Y
CASQ2_HUMAN	301	LS	I	L	W	I	D	P	D	F	L	L	V
CASQ2_MOUSE	301	LS	I	L	W	I	D	P	D	F	L	L	V
CASQ2_HUMAN	351	DL	P	T	A	E	E	L	E	D	W	I	E
CASQ2_MOUSE	351	DL	P	T	A	E	E	L	E	D	W	I	E
CASQ2_HUMAN	387	E	D	N	D	S	D	D	D	D	D	D	E
CASQ2_MOUSE	401	D	E	D	N	E	D	S	D	D	D	D	N

# Sequence alignment

## Rat

Pairwise Alignment Result

LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
2812	10414.5	1965/2812 (69.9%)	1965/2812 (69.9%)	430/2812 (15.3%)

NM_001232.3	1	AGCTTGGCTGTTTTTCTACTCTCATGCGTGCCTGCGTGCCTGCGTGTGTG	50
NM_017131.2	0	-----	0
NM_001232.3	51	TGTGTGTGTGCCCTGCTCTTTGTCCTGAGCCACGATTCCAGAGCTGGC	100
NM_017131.2	1	-----TTTGTCTGAGCCCAACTACACAGCC-GC	30
NM_001232.3	101	TGGACCCAAGGAGGTGAAG--AGTCATTTTCAGCCCCAGGAAGGGCAA	148
NM_017131.2	31	AGGA-CCAAGGAGGTGAGATCAGCCTCTTT--GTCCCTAACCAAGCTTA	77
NM_001232.3	149	GAAAGAGAAAAATCAGCCTGTCTGCTCTCTCCTTGGCTCAACAAGGCCTC	198
NM_017131.2	78	GCAGCG-----TCTCCAAG---AAC---CTTC	98
NM_001232.3	199	TAAACAGTCTTC--TGTCTCTATTCTGCACACGGCATATTTGGGAACGAG	246
NM_017131.2	99	CATCTGTCTTCCATGATCTCCGTTCTG-----GGGACTGAG	134
NM_001232.3	247	AAACAAAAGTTTTCCCAAATGAAGAGAACTCACTTGTATTATTGTGGGGAT	296
NM_017131.2	135	AAACAAGACTCTTCCCAAATGAAGAGGATTTACCTGCTCGTGGTGGGGCT	184
NM_001232.3	297	TTATTTTCTGTCCCTTTGCAGGGCAGAAGAGGGGCTTAATTTCCCCACAT	346
NM_017131.2	185	TTATCTGCTCTCCTTACGAGGGCAGAAGAGGGGCTGAACCTCCCCACGT	234
NM_001232.3	347	ATGATGGGAAGGACCGAGTGGTAAGTCTTTCCGAGAAGAACTCAAGCAG	396
NM_017131.2	235	ACGATGGGAAGGACCGAGTGGTCAGCCTTTCTGAGAAGAACTTGAAGCAA	284

## Mouse

Pairwise Alignment Result

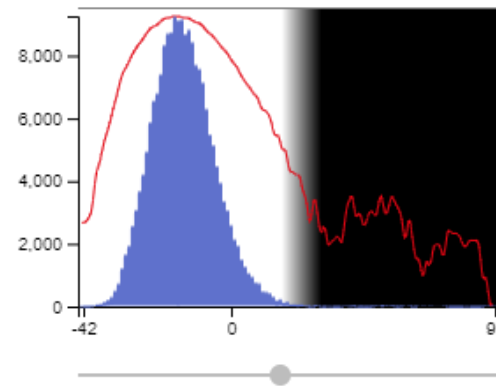
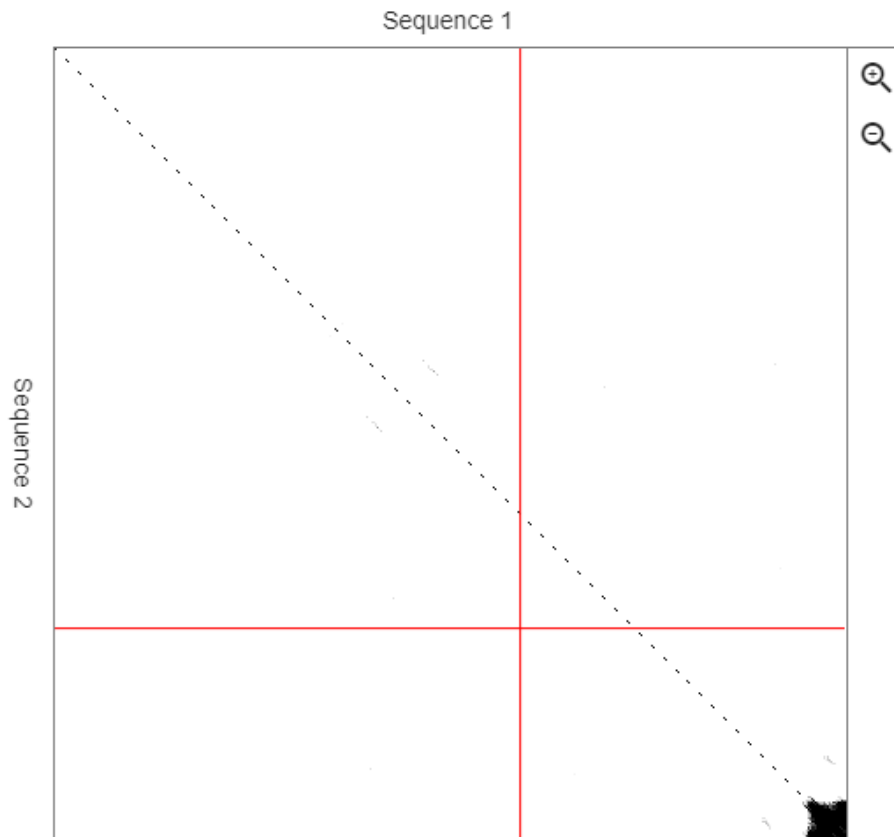
LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
2817	10634.0	2009/2817 (71.3%)	2009/2817 (71.3%)	374/2817 (13.3%)

NM_001232.3	1	AGCTTGGCTGTTTTTCTACTCTCATGCGTGCCTGCGTGCCTGCGTGTGTG	50
NM_009814.3	1	-----CTCTGC-----TCTGTGCGCATGTG	21
NM_001232.3	51	TGTGTGTGTGCCCTGCTCTTTGTCCTGAGCCACGATTCCAGAGCTGGC	100
NM_009814.3	22	TGCATTTGAGCCTCCACAGTTTGTCTGAGCCACGACTACACAGCT-GC	70
NM_001232.3	101	TGGACCCAAGGAGGTGAAGAGTCACTTTTCAGCCCCAGGAAGGGCAAAGA	150
NM_009814.3	71	AGGA-CCAAGGAGGTG-----	85
NM_001232.3	151	AGAGAGAAAAATCAGCCTGTCTGCTCTCTCCTTGGCTCAACAAGGCCTCTA	200
NM_009814.3	86	-----AAAGCAGCCTTTTGTCCCTC---AC-CAACAT---CTCTA	120
NM_001232.3	201	ACAGTCTTGTCTCTATTCT--TGCACACGGCATATT-TGGGAAC-GAG	246
NM_009814.3	121	AGAACCTTCCATCCTGTCTTCCATGATCTC---TATTC TGGAGACTGAG	166
NM_001232.3	247	AAACAAAAGTTTTCCCAAATGAAGAGAACTCACTTGTATTATTGTGGGGAT	296
NM_009814.3	167	AAGCAAGACTTTTCCCAAATGAAGAGGATTTACCTGCTCATGGTGGGGT	216
NM_001232.3	297	TTATTTTCTGTCCCTTTGCAGGGCAGAAGAGGGGCTTAATTTCCCCACAT	346
NM_009814.3	217	TTATCTGCTGTCTCCTGAGCGGGCAGAAGAGGGGCTGAACCTCCCCACGT	266
NM_001232.3	347	ATGATGGGAAGGACCGAGTGGTAAGTCTTTCCGAGAAGAACTCAAGCAG	396
NM_009814.3	267	ACGATGGGAAGGACCGAGTGGTCAGCCTTTCTGAGAAGAACTCAAGCAG	316

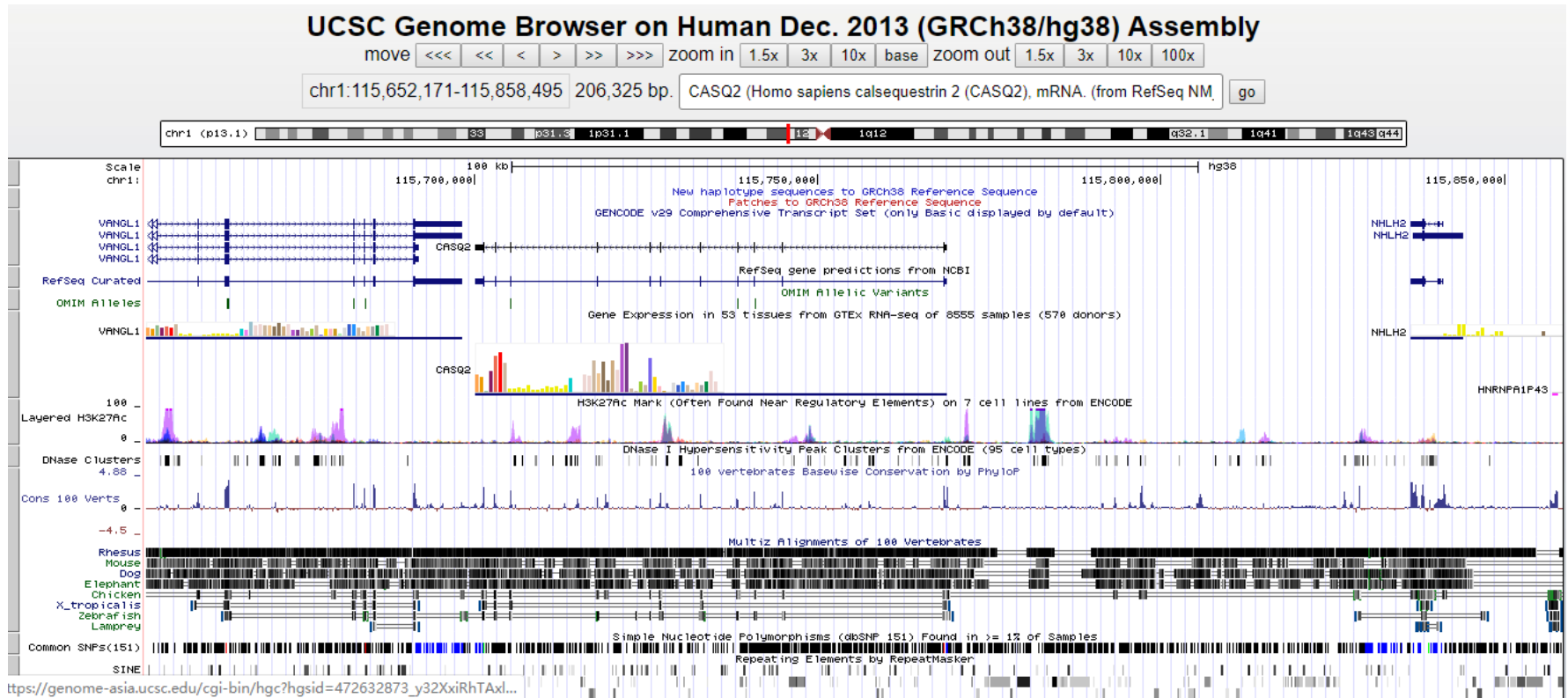
# Amino acid repeats analysis via Dotlet

SEQUENCE 1      SEQUENCE 2      Window size 15      Scoring matrix BLOSUM 62

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WLEEVKHTQTHNTHYDROWKRESEKNIKVEVDFETFDIDETWIKNKYEEELVEV  
VKEHQRPTRLRRLRPEEMFETWEDDLNGIHIVAFAEKSDPDGYEFLEILKQVARDNTDNP  
LSILWIDPDDFLLVAYWEKTFKIDLFRPQIGVVNVTDADSVWMEIPDDDDLPTAELED  
WIEDVLSGKINTEDDDDDDDNSDEEDNDDSDDDDE
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# Promoter prediction via different tools



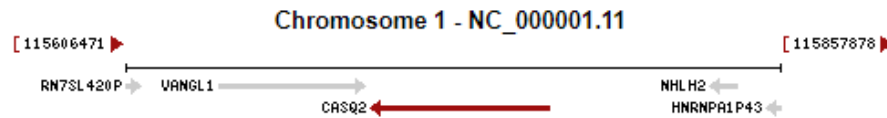
# Promoter prediction via different tools

Location: 1p13.1

See CASQ2 in [Genome Data Viewer](#)

Exon count: 11

Annotation release	Status	Assembly	Chr	Location
<a href="#">109</a>	current	GRCh38.p12 ( <a href="#">GCF_000001405.38</a> )	1	NC_000001.11 (115700003..115768805, complement)
<a href="#">105</a>	previous assembly	GRCh37.p13 ( <a href="#">GCF_000001405.25</a> )	1	NC_000001.10 (116242624..116311426, complement)



# Promoter prediction via different tools

## Homo sapiens chromosome 1, GRCh38.p12 Primary Assembly

NCBI Reference Sequence: NC\_000001.11

[GenBank](#) [Graphics](#)

>NC\_000001.11:115698003-115700003 Homo sapiens chromosome 1, GRCh38.p12 Primary Assembly

```
TACTTACATTCATAAGGTTTATGCTATGAACTTCTTCTCATTGTGATGTCAGTAAACAGAGTTAGTGTCT
CTGATGGAATAGTGTACCTGTCCACCAAAGTATTTTTGTTCCTTTTGGGTCCTCCAGTATAATCCCCCCC
TCATCCCAATTAACGTAAAATGTTTTACACATCACATTTTTATACTGTAAACTTGGAAAAAACTGA
AATATCAAATTTGTCTTGTCTTTCTTTCATGTGATTATTTCAATCTAAAAAGTTGCTTACTTTTTCA
GGGACATTTTTCACTCTCGCATAATTTGAGACCTTCAGAATTTCAAGACAACCTGTCATATTTCTATAA
AAACCAAGACAATTTGTGATGGATTGGGAAAGTAGAATTACCATTGTAACAAAACTACTAGTTGTCAATC
ATTTTACAGTGAAGAAAAATGTTTTGAATAGATAACTAAAAATGAAATCCTCAGGCTCTAAAAACATGGAGA
TGAACAGATCTTTTGGTAAACAGCAAGTGGAAAGGATTTGAGTCAAATAAGAAGACAGAAAAAGTAA
CAGACTTTGGGTTGATGTGGGAGGTGAATATTGGATTATTTTCTGAGTGGCTTGGGAATCAAGTTAAA
TTATCAACTGATTTTAGATAGGTCTATTTAAAGGAAATTTGATTATTTGCAAAGAAATATGAAGCCGTGT
TTCCGCTAACCTCAGTGGTAGAATTTGACAGCACACAATCAAATCTTAGCTATTGCATGGACAGAAAT
TAGAGAAAGCAATTGACTCAAAGATATTCATTGGTTAGATTATTGATAAGCTGTTTTCTTTGGGCCATTAA
GCAAAATGTACACAATTTATATCTACATAAGTAAACCTGCTAATACACTTTGTGCTATCATTGGATAT
TTGTTCCACCAAATCCCCTGTTGAAATTTAATCCCAGTGCAGGAGTATTGAGAGGTAGGGTCTAAAGG
GAGTGATTTAAGAACTTGAGAACTTGGGTCTGGGTGATGGATGATCTTTTATGAATAGATGAATGCCCTCTG
GAGGAAGTGGGGTGTGAGTGGGTACTCGCTCTGTTAGTTCCCTGGAGAGCTGTTGTTAGAGGCTGGCAC
CTCCTCTCTCATGCTTCTCTCTCACCATGTGATCTCTGCACACACTGGTTTTCTTTACCTTCTGCC
ATGAATGGAAAGCAGCCAAGGCTTTCACCTGATGCCAGTATTGCAGCCAGCAGAATTGTGAGCGAAATAA
ATATTTTTCTTCATAAAATACCCACTCTTAGTTATTTCTTTATATCAATAAAAAACAGACTAAGACACCT
TGTAAAGCTCTGTTACCCAATAGTGTGAGGAAATTAAGGATTCTAGTTAATCAATTATTATCCACCAA
CTCAATAAATGAGTATCTACTTTGTGATGGCAAAGCGCTAAGTGTAGGGATTCTAAGATAAATTCCTT
GCCTCTAAGGAGCCTGCAATTTAGTAAAAGGACAGACATGCAAAATATATGTTATACCTTAAATGATAAGT
GACATGATCCAGGGATGCACAAATCACAGGGGGGAAAGGGGACCTTCAGGTCACCTAGACAATTTGGATAA
ATGGTGCTATCACCCACCAAACCTAGGACTCCATGAAGAGGAGAAGATGTTTAGGGGAGAAGGCAATGAG
TTCAGGTTTTGTTGTGTTGAGTCTGAAAGTGTGTGTACAACAACAAGTCAAGATATCCAGAGGCAGTTGAA
TGAATGTGTCTAAAAATAAGGCAAGGAGTCAAGGTAGAGACTCATATTTGGAGGTAATTAGCACATGGA
TAGTATTGATGGGCACGATGACATCATTTTGGAAAGATATGTAGAGTTGAGATGCTGTGAAACACCATCA
TTCAAAGAGCAGGACAGAGGAAAGAGGGGCTAGAAAAGGAAAAATAGAGAAGAAATAAGGAGGTAGGACTGGAG
CCAGATGAGAATGAGCAGAGTCAAAAAATCAAGATAGGAT
```

### Change region shown

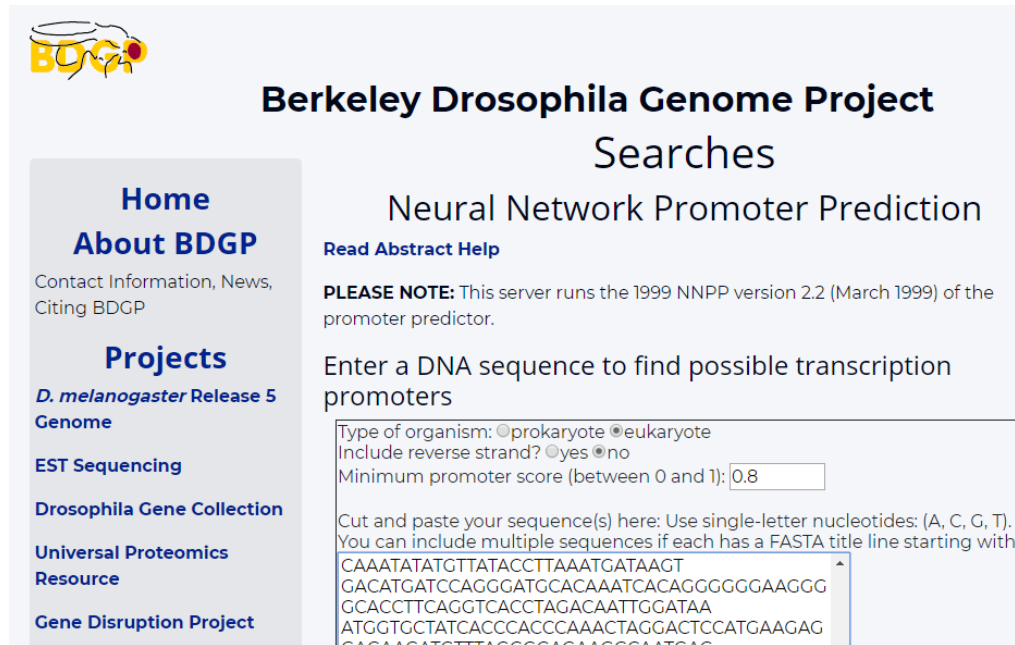
Whole sequence (abbreviated view)

Selected region

from:  to:



# Promoter prediction via different tools



The screenshot shows the Berkeley Drosophila Genome Project (BDGP) website interface for the Neural Network Promoter Prediction tool. The page title is "Berkeley Drosophila Genome Project Searches Neural Network Promoter Prediction". A sidebar on the left contains navigation links: Home, About BDGP, Projects (with sub-links for D. melanogaster Release 5 Genome, EST Sequencing, Drosophila Gene Collection, Universal Proteomics Resource, and Gene Disruption Project), and other resources. The main content area includes a "Read Abstract Help" link, a "PLEASE NOTE" section stating the tool uses the 1999 NNPP version 2.2, and a form for entering a DNA sequence. The form includes radio buttons for organism type (prokaryote/eukaryote), a checkbox for including the reverse strand, and a text input for the minimum promoter score (set to 0.8). A text area contains a sample DNA sequence with a FASTA header line.

## Promoter predictions for NC\_000001.11:115698003-115700003 :

Start	End	Score	Promoter Sequence
117	167	0.92	GGGTCCTCCAGTATAAATCCCCCCTCATCCCAATTAAGTGTAAAATGTTT
336	386	0.87	GTCATATTTCTATAAAAACCAAGACAATTGTGATGGATTGGGAAAGTAGA
1751	1801	0.99	TGAATGTGTCTAAAAATAAGGCAAGGAGTCAAGGTTAGAGACTCATATTT

# Promoter prediction via different tools

DTU Bioinformatics  
Department of Bio and Health Informatics  
[Home](#)

## Promoter 2.0 Prediction Server

Promoter2.0 predicts transcription start sites of vertebrate PolII promoters in DNA sequences. It has been developed as a tool for predicting promoters in genomic regions. It builds on principles that are common to neural networks and genetic algorithms.

[Instructions](#) [Output format](#)

**SUBMISSION**

Paste a single sequence or several sequences in [FASTA](#) format into the field below:

```
>NC_000001.11:115698003-115700003 Homo sapiens chromosome 1,
GRCh38.p12 Primary Assembly
TACTTACATTATAAGGTTTATGCTATGAACTTCTTCTCATTGTGATGTCAGTAACAGAG
```

Submit a file in [FASTA](#) format directly from your local disk:  
 No file chosen

Full output

## Promoter 2.0 Prediction Results

NC\_000001.11\_115698003-115700003 Homo sapiens chromosome 1, GRCh38.p12 Primary Assembly, 2001 nucleotides

Position	Score	Likelihood
1000	1.310	Highly likely prediction

# Promoter prediction via different tools

WWW Promoter Scan

**NOTICE** This website will be decommissioned soon. The associated tools are no longer be available from this web site.  
Please contact [www-bimas@bimas.cit.nih.gov](mailto:www-bimas@bimas.cit.nih.gov) if you have any questions.

**Function:** Predicts Promoter regions based on scoring homologies with putative eukaryotic Pol II promoter sequences. The **analysis** is done using the PROSCAN Version 1.7 suite of programs developed by [Dr. Dan Prestridge](#). Information on PROSCAN, including details on obtaining a copy, is maintained at the [Advanced Biosciences Computing Center](#), University of Minnesota.

A DNA sequence is all that needs to be supplied. There are no optional parameters for PROSCAN.

**Please enter or paste a Nucleic Acid sequence to analyze (most [formats](#) accepted):**

```
AGGTAATTAGCACATGGA
TAGTATTGATGGGCACGATGACATCATTTTGGAAAGAGTATGTAGAGTTGAGA
TGCTGTGAAACACCATCA
TTCAAAGAGCAGGCAGAGGAAGAGGGGCTAGAAAAGGAAAAATAGAGAAGAAAT
AAGGAGGTAGGACTGGAG
CCAGATGAGAATGAGCAGAGTCAGAAAAATCAAGATAGGAT
```

Echo input sequence (generally [recommended](#))

**Be Forewarned!**  
**Patience is a virtue:** Analysis for a 10Kbp sequence may take as long as 5 minutes (or more)!

Credits: WWW implementation by [BIMAS](#) staff

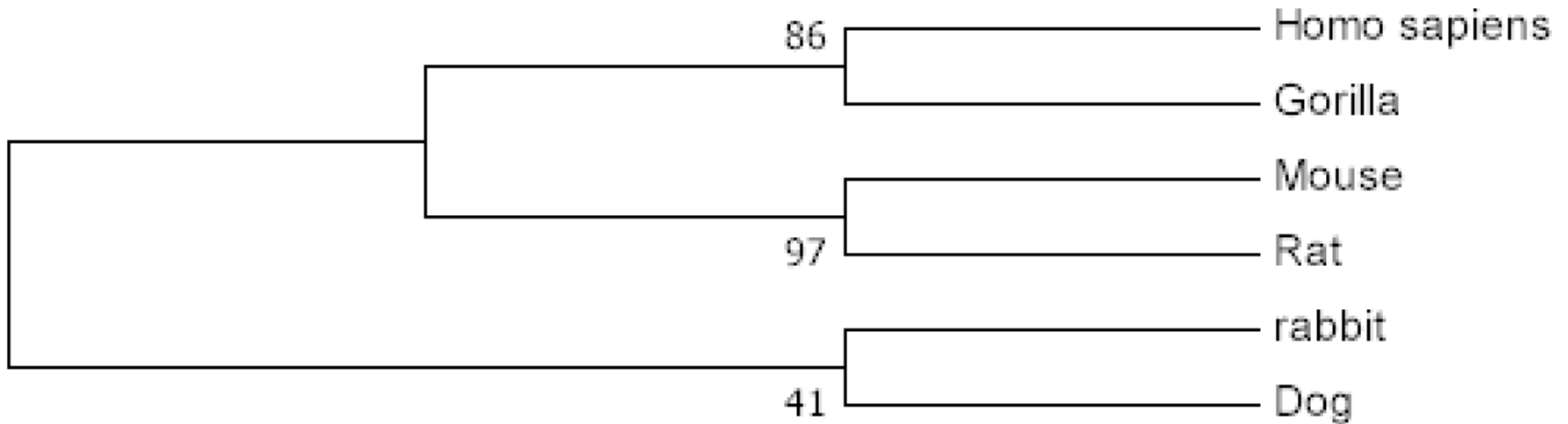
Proscan: Version 1.7  
Processed Sequence: 2001 Base Pairs  
**No promoter regions where predicted.**

# Phylogenetic tree construction

# Phylogenetic tree construction

Statistical Method: Neighbor-joining

Test of Phylogeny: Bootstrap method



# Structural analysis

# Human CASQ2 amino acid composition and theoretical pI

Number of amino acids: 399

Molecular weight: 46435.79

Theoretical pI: 4.21

A	21	5.30%	K	32	8.00%
R	11	2.80%	M	6	1.50%
N	11	2.80%	F	27	6.80%
D	53	13.30%	P	17	4.30%
C	2	0.50%	S	18	4.50%
Q	10	2.50%	T	13	3.30%
E	49	12.30%	W	5	1.30%
G	14	3.50%	Y	14	3.50%
H	6	1.50%	V	27	6.80%
I	25	6.30%	O	0	0.00%
L	38	9.50%	U	0	0.00%

Total number of negatively charged residues (Asp + Glu): 102

Total number of positively charged residues (Arg + Lys): 43

# Disulfide bonding prediction

```

.....10.....20.....30.....40.....50.....60.....70.....
AA      MKRTHLFIVGIYFLSSCRAEEGLNFPTYDGKDRVVSLSSEKNFKQVLKKYDLLCLYYHEPVSSDKVTQKQFQLKEIVLEL
DB_state      0                                0
DB_conf       6                                7

80.....90.....100.....110.....120.....130.....140.....150.....
AA      VAQVLEHKAIGFVMVDAKKEAKLAKKLGFDDEESLYILKGDRTIEFDGEFAADVLFVFLLDLIEDPVEIISSKLEVQAF
DB_state
DB_conf

.160.....170.....180.....190.....200.....210.....220.....230.....
AA      ERIEDYIKLIGFFKSEDSEYYKAFEEAAEHFQPYIKFFATFDKGVAKKLSLKMNEVDFYEPFMDEPIAIPNKPYTEEEL
DB_state
DB_conf

..240.....250.....260.....270.....280.....290.....300.....310.....
AA      VEFVKEHQRPTRLRRLRPEEMFETWEDDLNGIHIVAFAEKSDPDGYEFLEILKQVARDNTDNPDLNILWIDPDDFPLLVA
DB_state
DB_conf

...320.....330.....340.....350.....360.....370.....380.....390...
AA      YWEKTFKIDLFRPQIGVNVTDADSVWMEIPDDDDLPTAAELEDWIEDVLSGKINTEDDDEDDDDDDNSDEEDNDDSD
DB_state
DB_conf

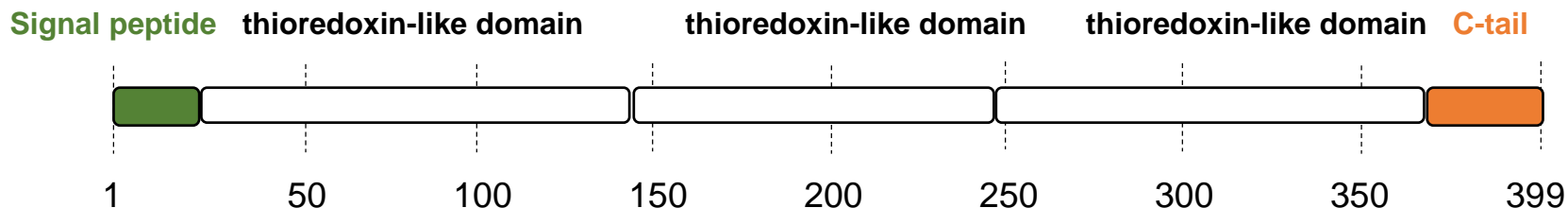
....
AA      DDDE
DB_state
DB_conf

```

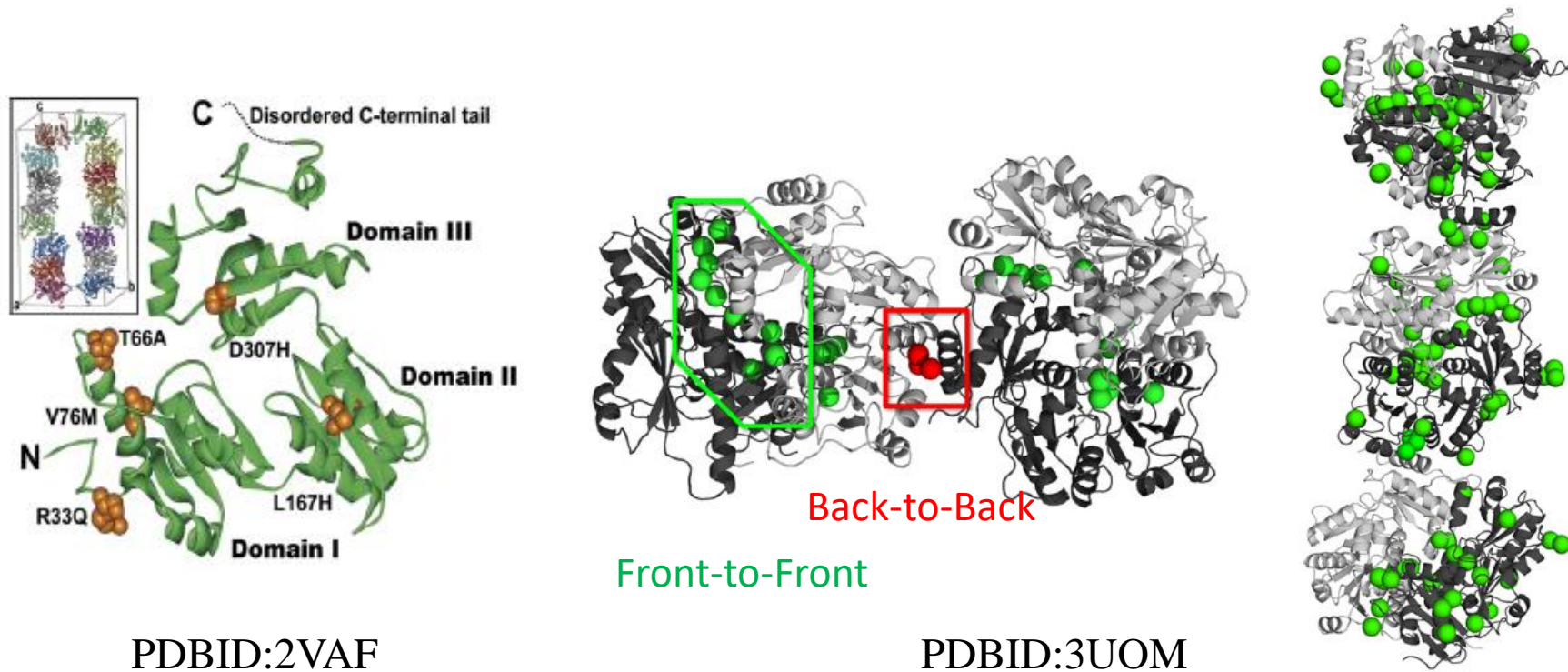
- **AA** amino acid sequence
- **DB\_state** predicted disulfide bonding state (1=disulfide bonded, 0=not disulfide bonded)
- **DB\_conf** confidence of disulfide bonding state prediction (0=low to 9=high)



# Domain Distribution and Structure of CASQ2



## Structure of CSQ2 with calcium bound



# Alignment of CASQ2 and CASQ1

## EMBOSS Water

```

CASQ2_HUMAN 15 SSCRAEEGLNFPTYDGKDRVVSLSSEKNFKQVLLKKYDLLCLYYHEPVSSDK 64
|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|
CASQ1_HUMAN 30 SGVQGQEGLDPEYDGVDRVINWNAKNYKNVFKKYEVLLALLYHEPPEDDK 79
CASQ2_HUMAN 65 VTQKQFQLKEIVLELVAQVLEHKAIGFVMDAKKEAKLAKKLGDFDEEGL 114
.:|:|:|:|:|:|:|:|:|:|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|:
CASQ1_HUMAN 80 ASQRQFEMEELILELAAQVLEDKGVGFLVDSEKDAAVAKKLGLETVDSM 129
CASQ2_HUMAN 115 YILKGDRTIEFDGFEAADVLEFLLDLIEDPVEIISSEKLEVQAFERIEDY 164
|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|
CASQ1_HUMAN 130 YVFKGDEVIEYDGEFSADTIVEFLLDVLEDPVELIEGERELQAFENIEDE 179
CASQ2_HUMAN 165 IKLIGFFKSEDSEYYKAFEEAAEHFQPYIKFFATFDKGVAKKLSLKMNEV 214
|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:
CASQ1_HUMAN 180 IKLIGYFKSKDSEHYKAFEDAAEEFHPYIPFFATFDSKVAKKLTCLKNEI 229
CASQ2_HUMAN 215 DFYEPFMDEPIAIPNKPYTEEELVEFVKEHQRPTRLRRLRPEEMFETWEDD 264
|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:
CASQ1_HUMAN 230 DFYEAFMEEPVTIPDKPNSEEEIVNFVEEHRSTLRKLPESMYETWEDD 279
CASQ2_HUMAN 265 LNGIHIVAFAEKSDPDGYEFLEILKQVARDNTDNPDLISLWIDPDDFPLL 314
.:|:|:|:|:|:|:|:|:|:|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|:
CASQ1_HUMAN 280 MDGIHIVAFAEADPDGFLETLKAVAQDNTENPDLISIIWIDPDDFPLL 329
CASQ2_HUMAN 315 VAYWEKTFKIDLFRPQIGVWVWTDADSVWMEIPDDDLPTAEELDWIED 364
|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|
CASQ1_HUMAN 330 VPYWEKTFDIDLAPQIGVWVWTDADSVWMEMDDEEDLPSAEELDWLED 379
CASQ2_HUMAN 365 VLSGKINTEDEDDDDDD 381
|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|
CASQ1_HUMAN 380 VLEGEINTEDEDDDDDD 396

```

Identity: 251/367 (68.4%)  
 Similarity: 316/367 (86.1%)  
 Gaps: 0/367 (0.0%)  
 Score:1412.0

## EMBOSS Needle

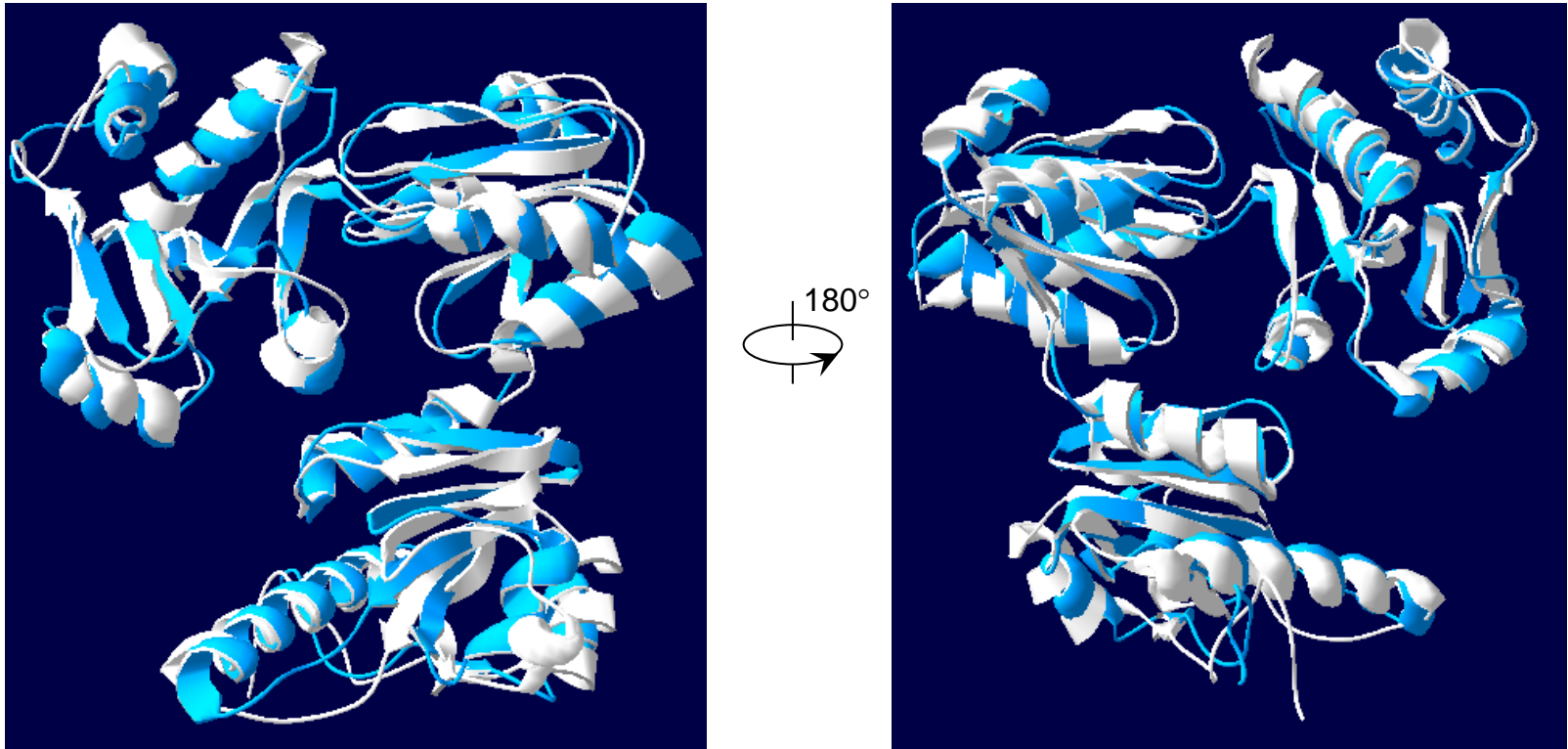
```

CASQ2_HUMAN 1 -----MKRTHLFIIVGIYFLSSCRAEEGLNFPTYDGKDRV 34
|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|
CASQ1_HUMAN 1 MSATDRMGPRAPVPLRLALLLLLVLGTP-KSGVQGQEGLDPEYDGVDRV 49
CASQ2_HUMAN 35 VSLSEKNFKQVLLKKYDLLCLYYHEPVSSDKVTQKQFQLKEIVLELVAQVL 84
.:|:|:|:|:|:|:|:|:|:|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|:
CASQ1_HUMAN 50 INWNAKNYKNVFKKYEVLLALLYHEPPEDDKASQRQFEMEELILELAAQVL 99
CASQ2_HUMAN 85 EHKAIGFVMDAKKEAKLAKKLGDFDEEGLYILKGDRTIEFDGFEAADVLE 134
|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|
CASQ1_HUMAN 100 EDKGVGFLVDSEKDAAVAKKLGLETVDSMYVFKGDEVIEYDGEFSADTI 149
CASQ2_HUMAN 135 VEFLLDLIEDPVEIISSEKLEVQAFERIEDYIKLIGFFKSEDSEYYKAFEE 184
|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:
CASQ1_HUMAN 150 VEFLLDVLEDPVELIEGERELQAFENIEDEIKLIGYFKSKDSEHYKAFED 199
CASQ2_HUMAN 185 AAHFQPYIKFFATFDKGVAKKLSLKMNEVDFYEPFMDEPIAIPNKPYTE 234
|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|:|:|:|. . . .|
CASQ1_HUMAN 200 AAEEFHPYIPFFATFDSKVAKKLTCLKNEIDFYEAFMEEPVTIPDKPNSE 249
CASQ2_HUMAN 235 EELVEFVKEHQRPTRLRRLRPEEMFETWEDDLNNGIHIVAFAEKSDPDGYEF 284
|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:|:
CASQ1_HUMAN 250 EEIVNFVEEHRSTLRKLPESMYETWEDDMDGIHIVAFAEADPDGFLEF 299
CASQ2_HUMAN 285 LEILKQVARDNTDNPDLISLWIDPDDFPLLVAWEKTFKIDLFRPQIGVW 334
|. . . .|:|:|:|. . . .|:|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:
CASQ1_HUMAN 300 LETLKAVAQDNTENPDLISIIWIDPDDFPLLVVYWEKTFDIDLAPQIGVW 349
CASQ2_HUMAN 335 NVTADADSVWMEIPDDDLPTAEELDWIEDVLSGKINTEDEDDDDDDDDN 384
|:|:|:|:|:|:|:|:|:|:|:|:|:|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:~|:
CASQ1_HUMAN 350 NVTADADSVWMEMDDEEDLPSAEELDWLEDVLEGEINTEDEDDDDDDDD--- 396
CASQ2_HUMAN 385 SDEEDNDDSDDDDDDE 399
CASQ1_HUMAN 397 ----- 396

```

Identity: 253/415 (61.0%)  
 Similarity: 321/415 (77.3%)  
 Gaps: 35/415 (8.4%)  
 Score:1405.0

# Structural comparison between CASQ1 and CASQ2

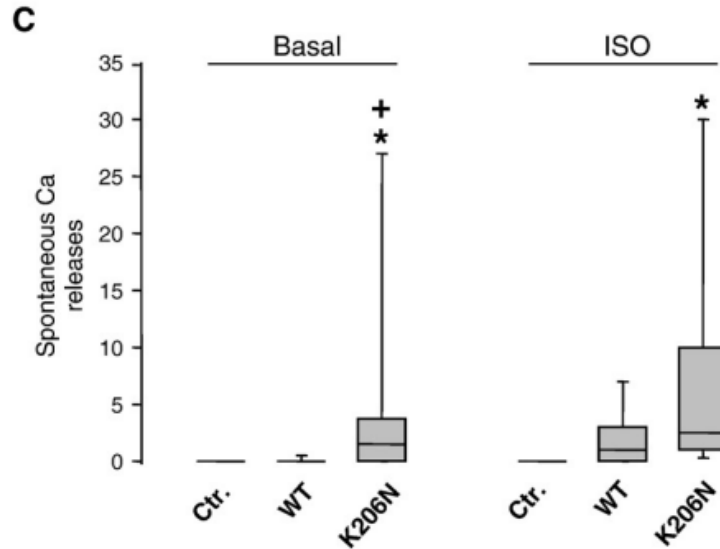
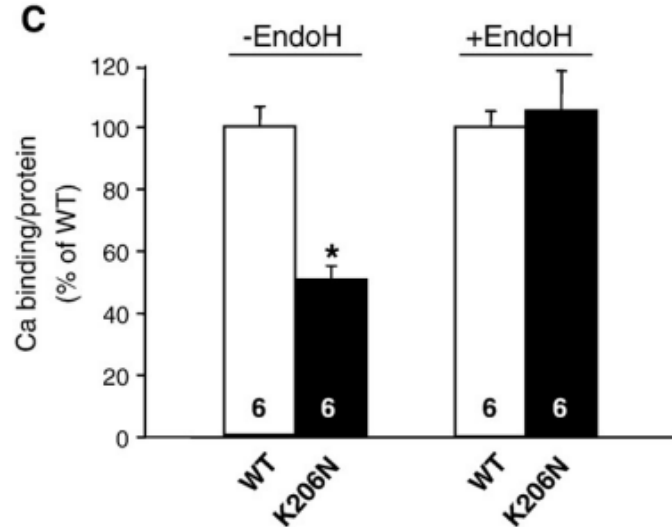
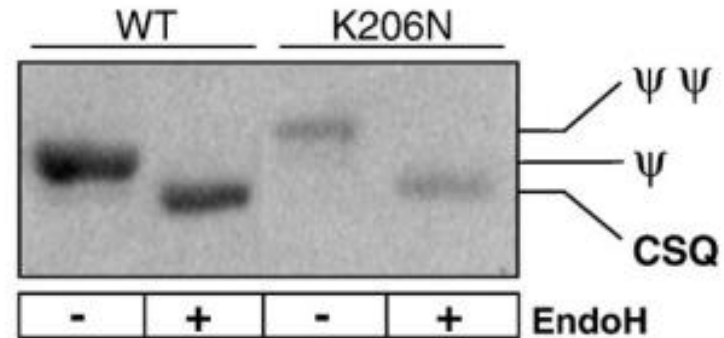


Human CASQ1 is colored blue, while human CASQ2 is colored white.

# CASQ2<sup>K206N</sup> contributes to decreased calcium binding and increased spontaneous calcium release

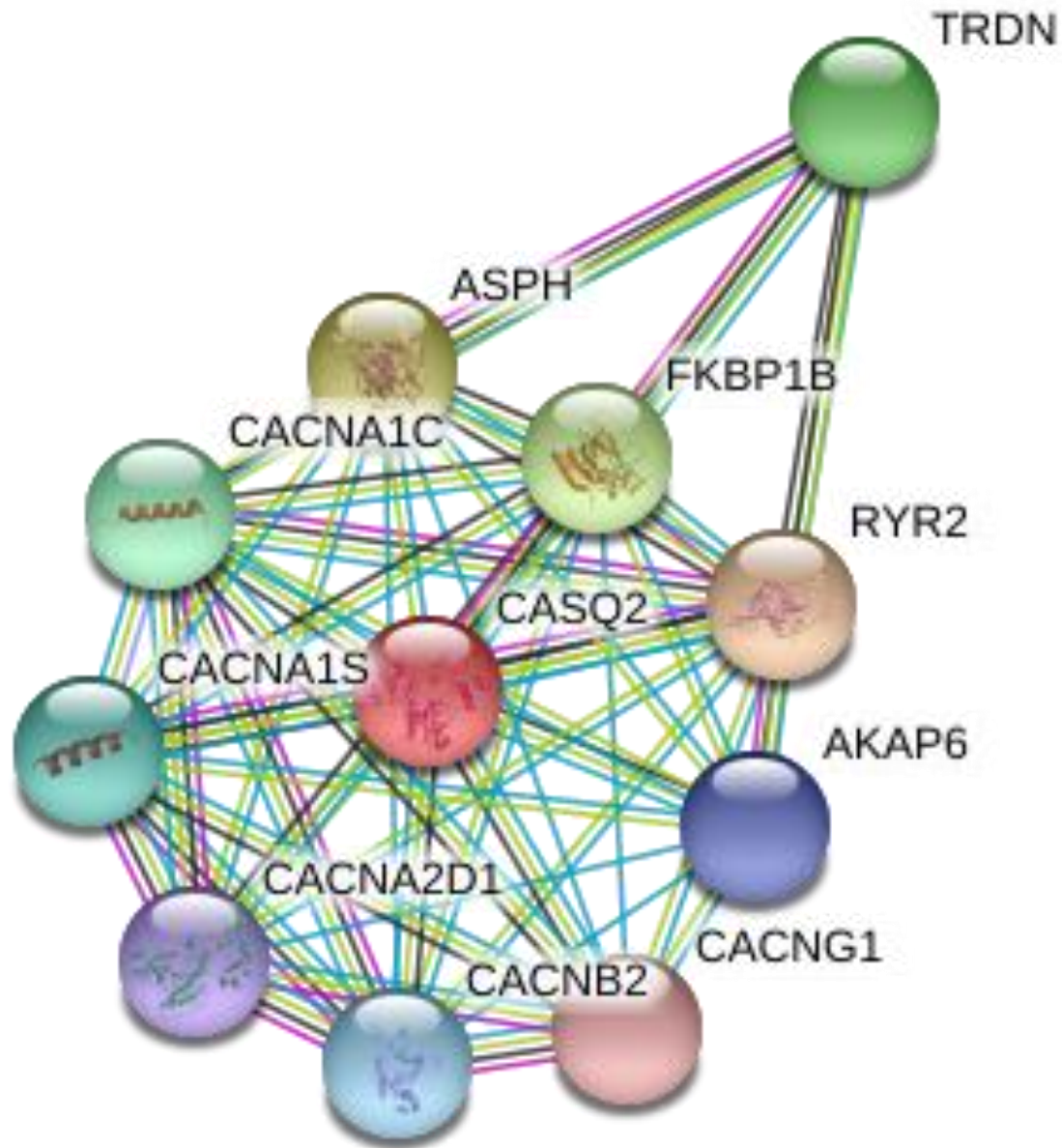
## CASQ2 (exon 6)

Human	FDKGVAK	<b>K</b>	LSLKMN
Rat	-----	K	-F-EV-
Mouse	---A---	K	-----
Rabbit	-----	K	-----
Dog	-----	K	-----
Human CASQ1	--SK---	<b>K</b>	-T--L-



# Functional analysis

# Network of protein-protein interactions



STRING

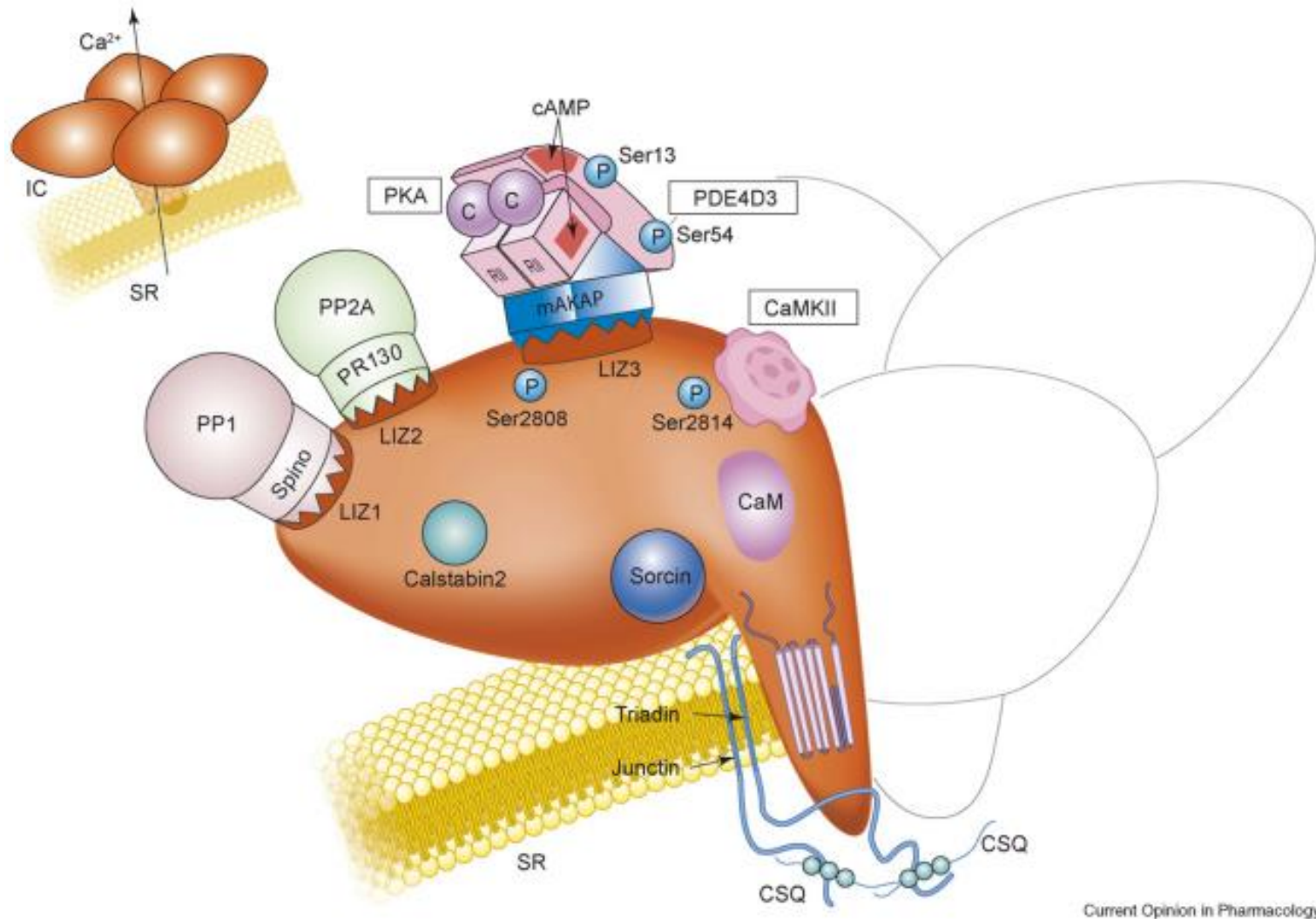
**Your Input:**

**CASQ2** *Calsequestrin 2 (cardiac muscle); Calsequestrin is a high-capacity, moderate affinity, calcium-binding protein and thus acts as an internal calcium store in muscle. Calcium ions are bound by clusters of acidic residues at the protein surface, especially at the interface between subunits. Can bind around 60 Ca(2+) ions. Regulates the release of luminal Ca(2+) via the calcium release channel RYR2; this plays an important role in triggering muscle contraction. Plays a role in excitation-contraction coupling in the heart and in regulating the rate of heart beats (399 aa)*

**Predicted Functional Partners:**

		Neighborhood	Gene Fusion	Cooccurrence	Coexpression	Experiments	Databases	Textmining	[Homology]	Score
<b>RYR2</b>	<i>Ryanodine receptor 2 (cardiac); Calcium channel that mediates the release of Ca(2+) from the sarcoplasmic reticulu...</i>				●		●	●		0.963
<b>ASPH</b>	<i>Aspartate beta-hydroxylase; Isoform 1- specifically hydroxylates an Asp or Asn residue in certain epidermal growth fa...</i>						●	●		0.949
<b>FKBP1B</b>	<i>FK506 binding protein 1B, 12.6 kDa; Has the potential to contribute to the immunosuppressive and toxic effects of FK...</i>						●	●		0.911
<b>TRDN</b>	<i>Triadin; Contributes to the regulation of luminal Ca2+ release via the sarcoplasmic reticulum calcium release channe...</i>				●	●	●	●		0.907
<b>CACNA1C</b>	<i>Calcium channel, voltage-dependent, L type, alpha 1C subunit; Voltage-sensitive calcium channels (VSCC) mediate th...</i>				●		●	●		0.826
<b>CACNA1S</b>	<i>Calcium channel, voltage-dependent, L type, alpha 1S subunit; Voltage-sensitive calcium channels (VSCC) mediate th...</i>				●		●	●		0.784
<b>CACNB2</b>	<i>Calcium channel, voltage-dependent, beta 2 subunit; The beta subunit of voltage-dependent calcium channels contrib...</i>				●		●	●		0.781
<b>AKAP6</b>	<i>A kinase (PRKA) anchor protein 6; Binds to type II regulatory subunits of protein kinase A and anchors/targets them t...</i>				●		●	●		0.753
<b>CACNA2D1</b>	<i>Calcium channel, voltage-dependent, alpha 2/delta subunit 1; The alpha-2/delta subunit of voltage-dependent calci...</i>						●	●		0.752
<b>CACNG1</b>	<i>Calcium channel, voltage-dependent, gamma subunit 1; This protein is a subunit of the dihydropyridine (DHP) sensitiv...</i>				●		●	●		0.746

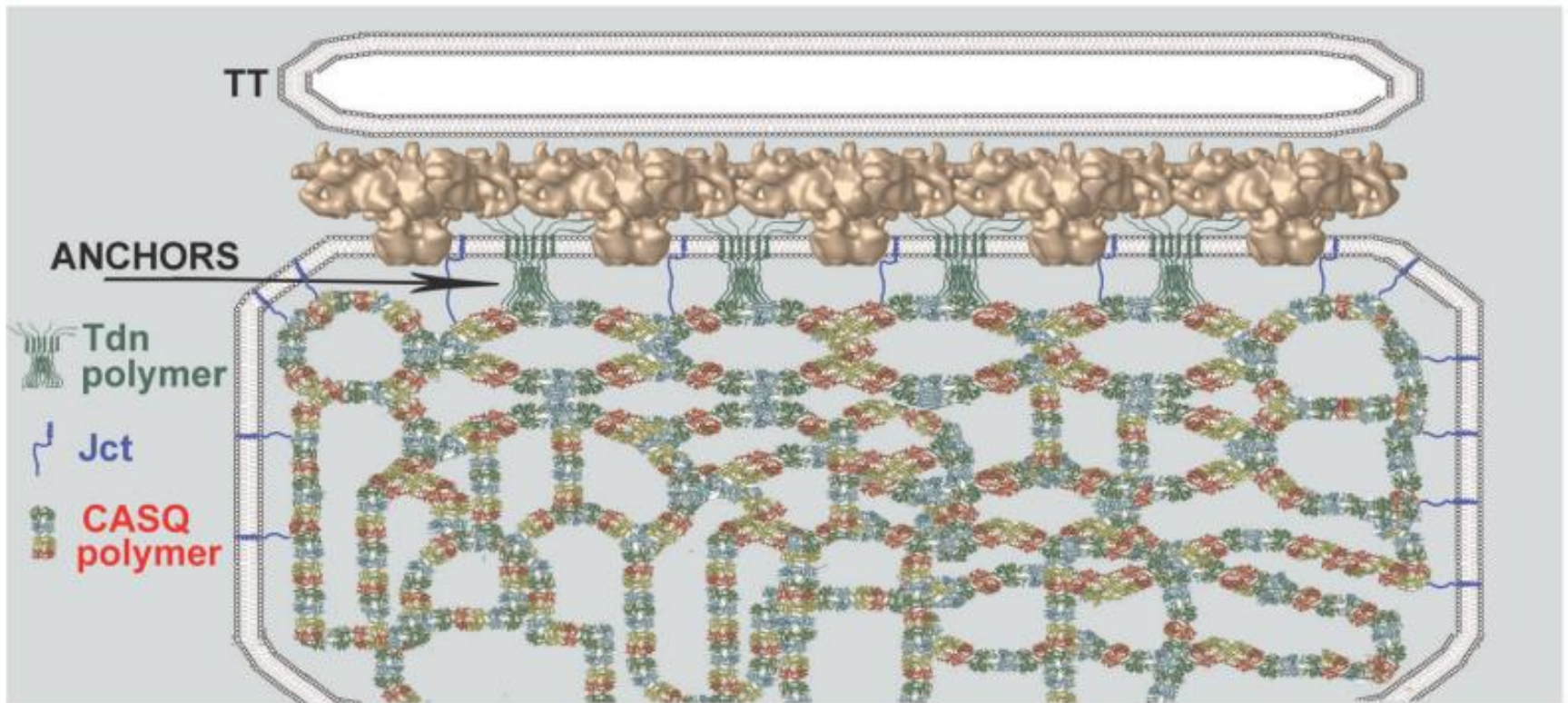
# Schematic graph of RyR2 and signaling complex



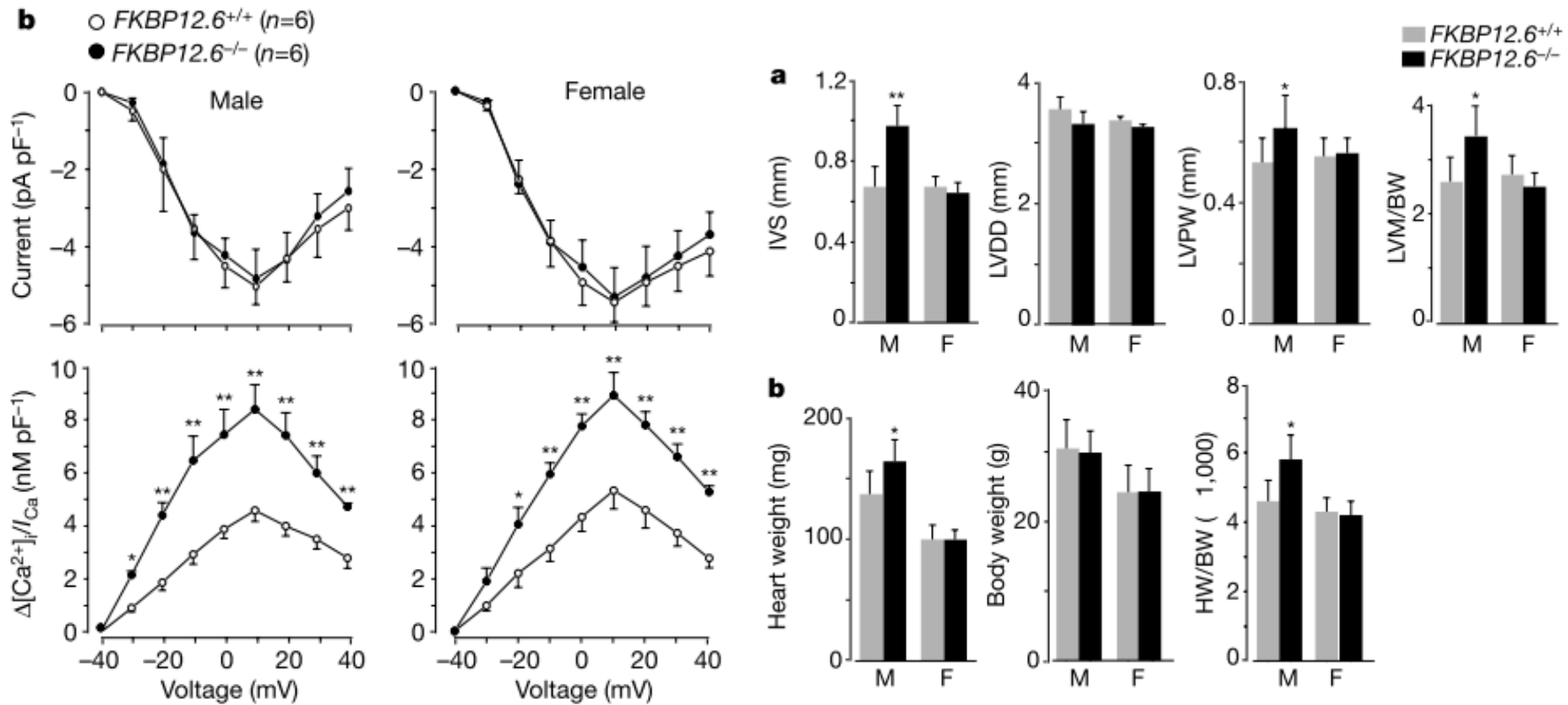
Current Opinion in Pharmacology



# A model proposing how CASQ2, RyR2, TRDN and JCTN function as a whole?



# FKBP12.6<sup>-/-</sup> mice suffer from cardiac hypertrophy and increased calcium transient



# Perspectives

# Therapeutic approaches for patients with CPVT

## Drug therapy

- β-blockers (e.g. Nadolol): first line therapy
- LCC blockers (e.g. Verapamil)
- RyR2 blockers (e.g. Flecainide)
- Combination might be better

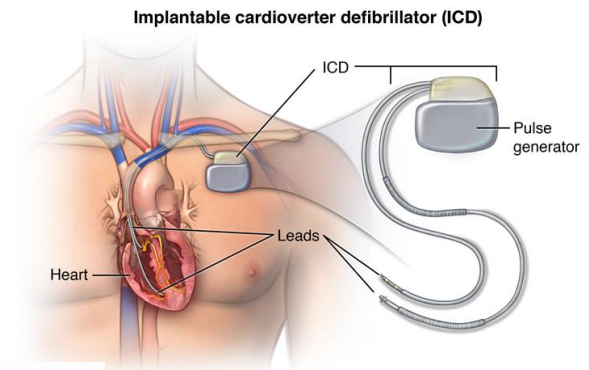


## Left cardiac sympathetic denervation

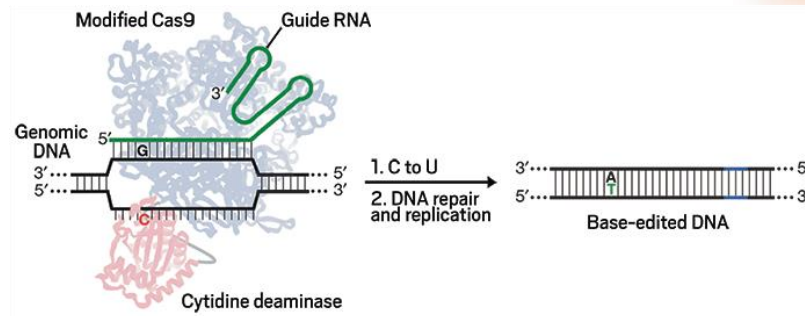
Effective, but surgery required, not universally available, and only tested in a small cohorts

## Implantable cardioverter-defibrillator

Potentially harmful effective in CPVT patients



## Gene therapy (Promising)



*Thank  
you*

