Mutation associated with an autosomal dominant cone-rod dystrophy CORD7 modifies RIM1-mediated modulation of voltage-dependent Ca2+ channels.

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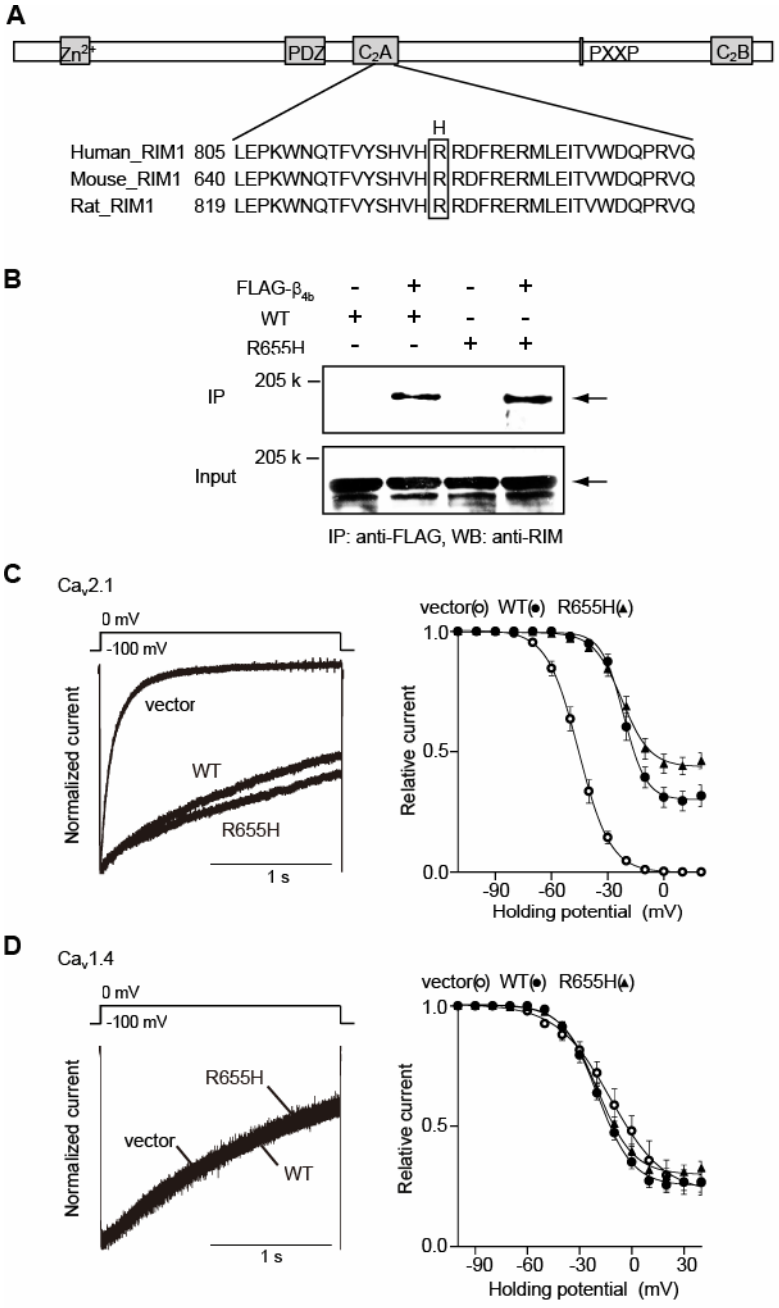
A
Zn2+
PDZ
C2A
PXXP
C2B
H
Human_RIM1 805 LEPKWNQTFVYSHVHRRDFRERMLEITVWDQPRVQ
Mouse_RIM1 640 LEPKWNQTFVYSHVHRRDFRERMLEITVWDQPRVQ
Rat_RIM1 819 LEPKWNQTFVYSHVHRRDFRERMLEITVWDQPRVQ
B
FLAG-β4b - + - +
WT + + - -
R655H - - + +
IP
205 k
Input
205 k
IP: anti-FLAG, WB: anti-RIM
C
Cav2.1
0 mV
-100 mV
vector
WT
R655H
1 s
Normalized current
vector(○) WT(●) R655H(▲)
1.0
0.5
0.0
Relative current
-90 -60 -30 0
Holding potential (mV)
D
Cav1.4
0 mV
-100 mV
R655H
vector
WT
1 s
Normalized current
vector(○) WT(●) R655H(▲)
1.0
0.5
0.0
Relative current
-90 -60 -30 0 30
Holding potential (mV)

Figure 1

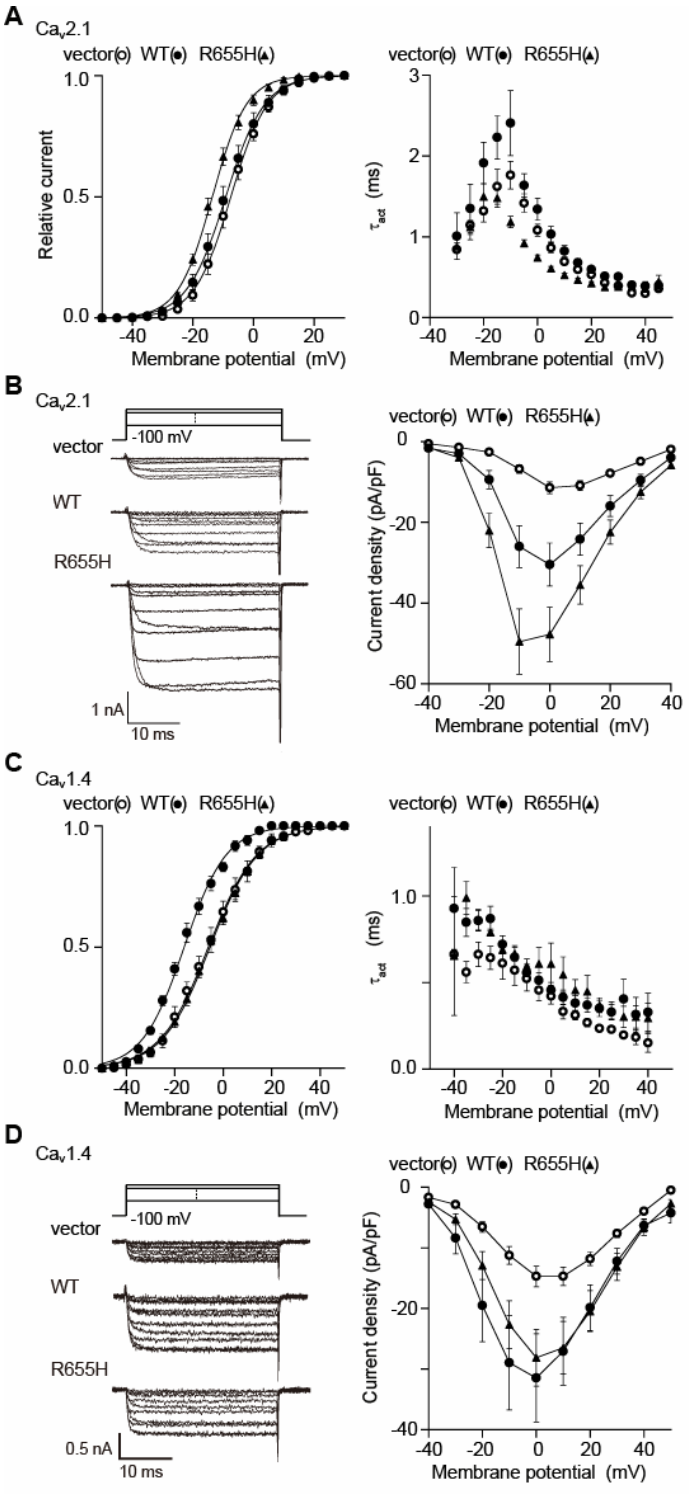
A
Cav2.1
vector(○) WT(●) R655H(▲)
Relative current
Membrane potential (mV)
τact (ms)
B
Cav2.1
vector
WT
R655H
-100 mV
1 nA
10 ms
Current density (pA/pF)
C
Cav1.4
D
Cav1.4
0.5 nA

Figure 2

Table 1 Effects of mouse $RIM1_{R655H}$ constructs on current density, activation, and inactivation of Cav2.1, or Cav1.4 channel [1)2)].

$Ca_v2.1$	Current density [3)]		Activation parameters [4)]				Inactivation parameters [5)]					
	(pA/pF)	S.E.	$V_{0.5}$	S.E.	k	S.E.	a	S.E.	$V_{0.5}$	S.E.	k	S.E.
vector	-11.43	1.48	-7.19	1.24	4.47	1.26	1.00	0.00	-45.90	1.77	-7.53	0.27
RIM1	-30.45	5.34 *	-9.11	1.55	5.57	0.23	0.70	0.04 ***	-21.26	1.24 ***	-5.63	0.65
$RIM1_{R655H}$	-47.73	6.71 ***$_{\#}$	-13.35	0.89 **$_{\#}$	5.07	0.16	0.57	0.03 ***$_{\#\#}$	-22.00	1.18 ***	-7.97	0.97 $_{\#}$

$Ca_v1.4$	Current density [3)]		Activation parameters [4)]				Inactivation parameters [5)]					
	(pA/pF)	S.E.	$V_{0.5}$	S.E.	k	S.E.	a	S.E.	$V_{0.5}$	S.E.	k	S.E.
vector	-14.71	1.71	-6.08	1.77	9.69	0.83	0.79	0.06	-10.50	3.40	-15.12	1.00
RIM1	-31.48	7.29 *	-16.16	1.02 ***	8.32	0.53	0.75	0.03	-19.54	1.78 *	-9.69	0.33 ***
$RIM1_{R655H}$	-28.13	4.70 *	-5.41	0.87 $_{\#\#\#}$	9.92	0.59	0.73	0.02	-18.00	1.56 *	-10.84	0.74 ***

1) $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ versus vector (ANOVA, Fisher's test).

2) $_{\#}P < 0.05$, $_{\#\#}P < 0.01$, $_{\#\#\#}P < 0.001$ versus RIM1 (ANOVA, Fisher's test).

3) Amplitude of Ba^{2+} currents evoked by depolarizing pulse to 0 mV from V_h of -100 mV are divided by capacitance.

4) $V_{0.5}$ is the half-maximal activation voltage, and k is the slope factor.

5) a is the rate of inactivating component, $V_{0.5}$ is the half-inactivation potential and k is the slope factor.