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Andersen-Tawil syndrome (ATS)

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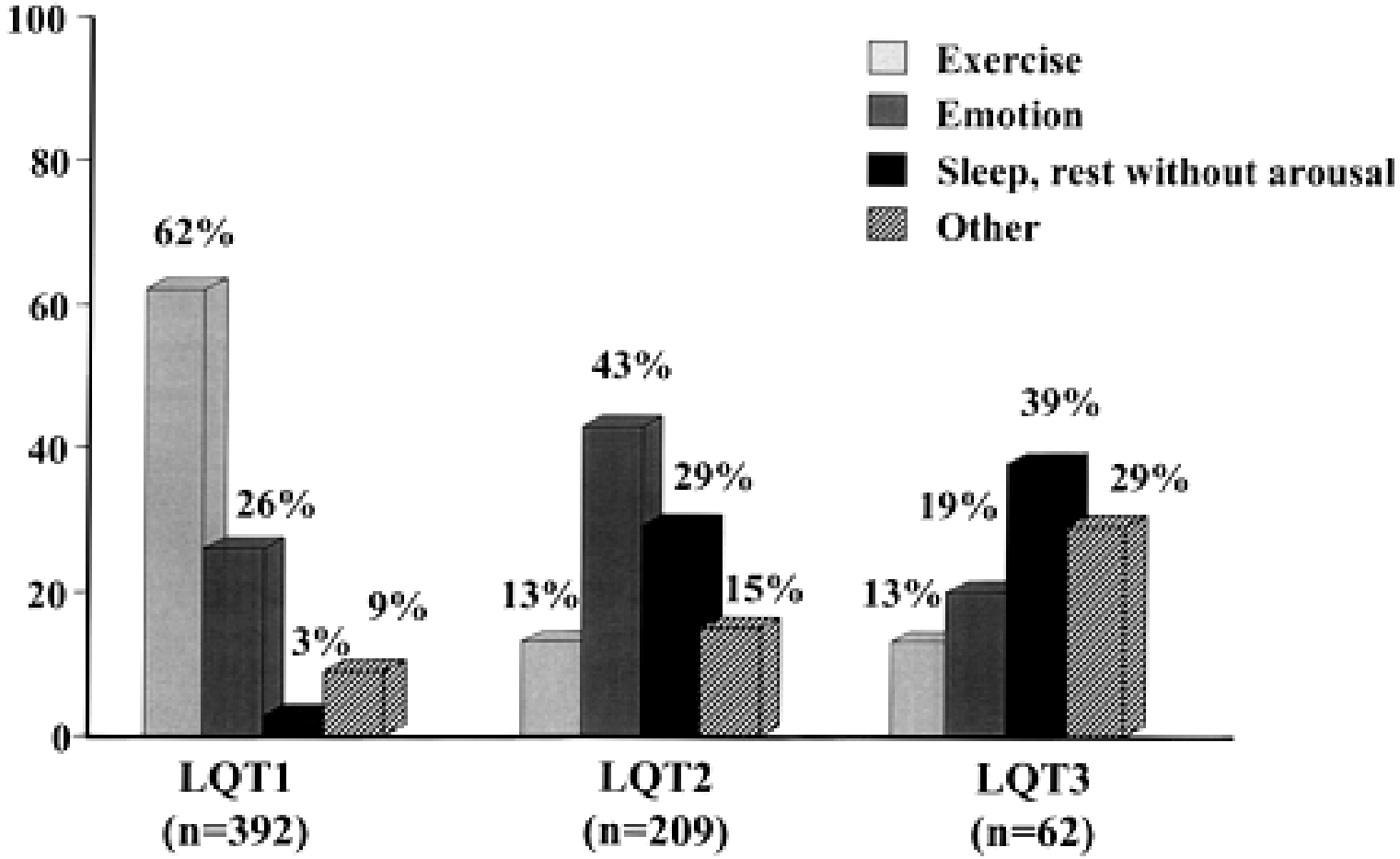
ATS

- normo- or dyskalemic periodic paralysis
- ventricular arrhythmia (LQT 7)
- slight dysmorphic features in some patients
- no myotonia
- dominant mutations in *KCNJ2* encoding the $K_{ir}2.1$ K+ channel

KCNJ2 expressed in skeletal and cardiac muscle

Long QT syndromes

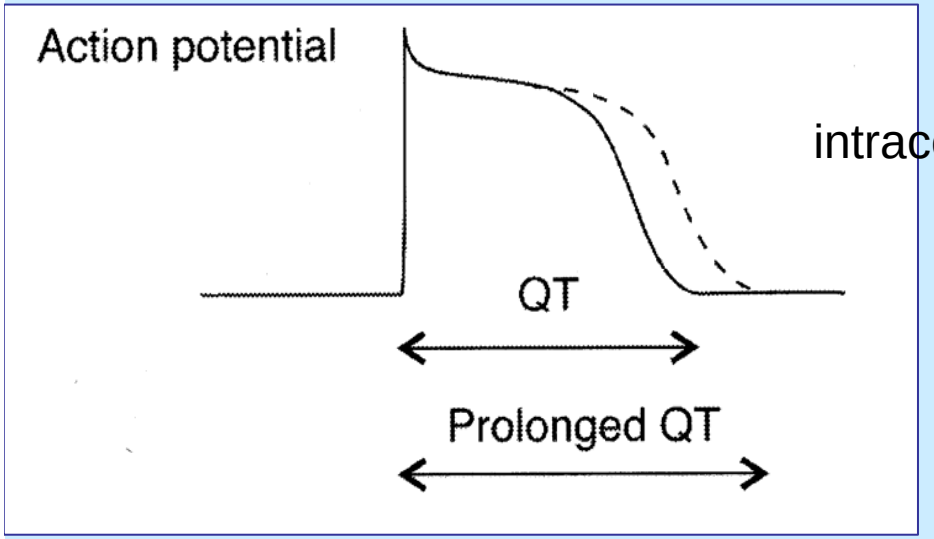
- episodic arrhythmias known as *torsade de points*
- conversion into ventricular fibrillation
- sudden death in young otherwise healthy individuals



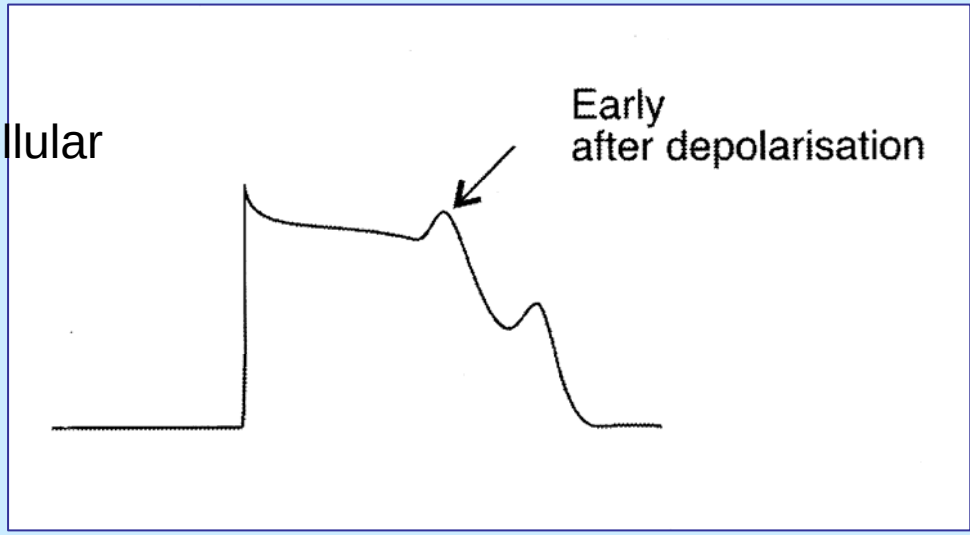
LQT7 is similar to LQT1

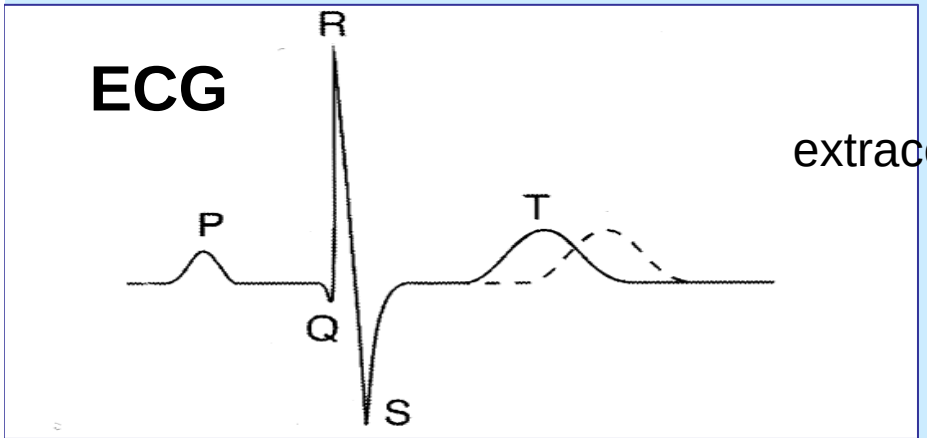
Development of LQT arrhythmia by prolonged action potential

Arrhythmia improves at slight tachycardia

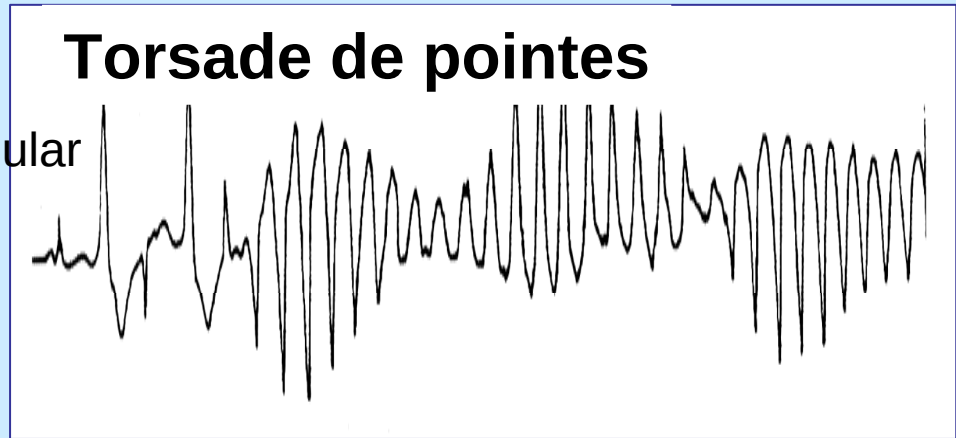


intracellular

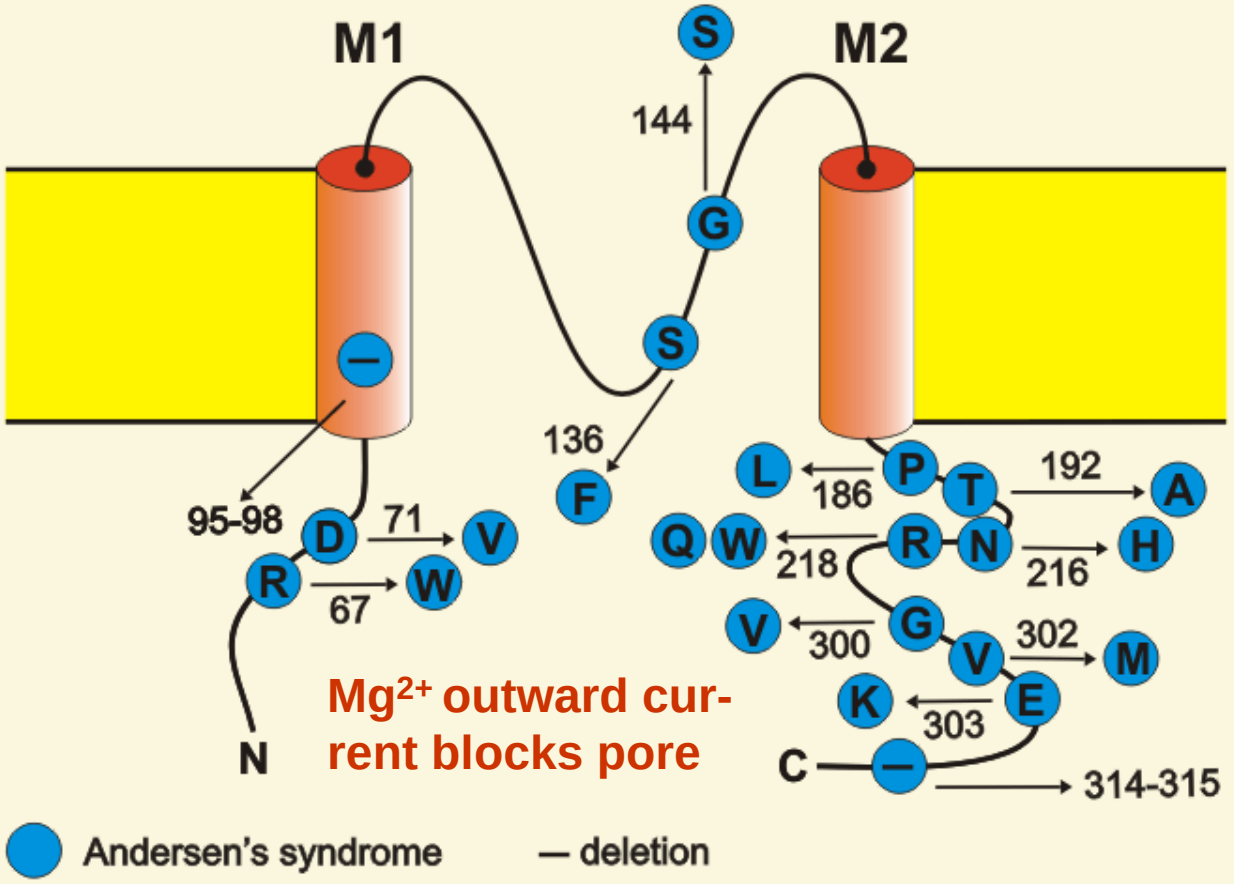




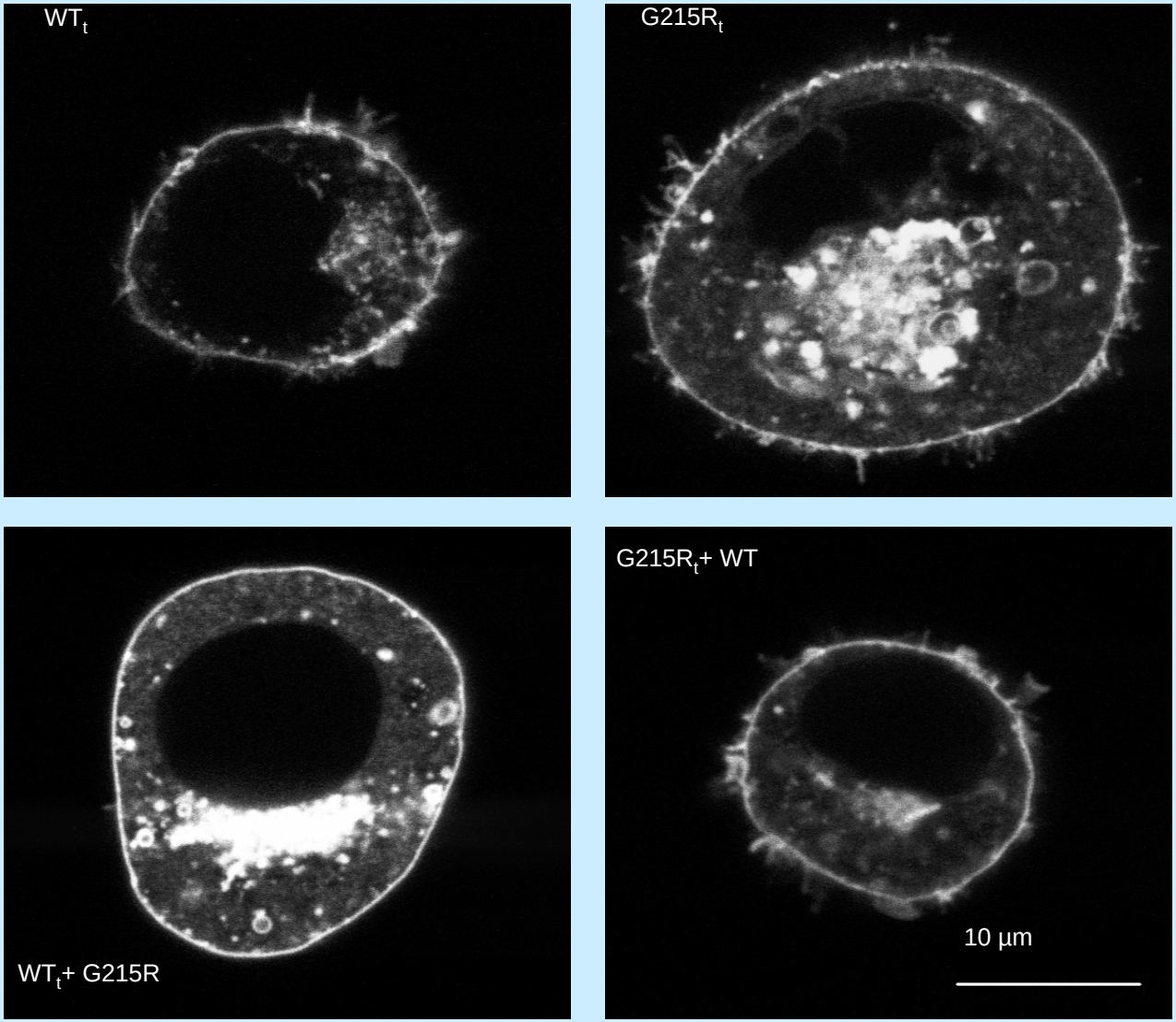
extracellular



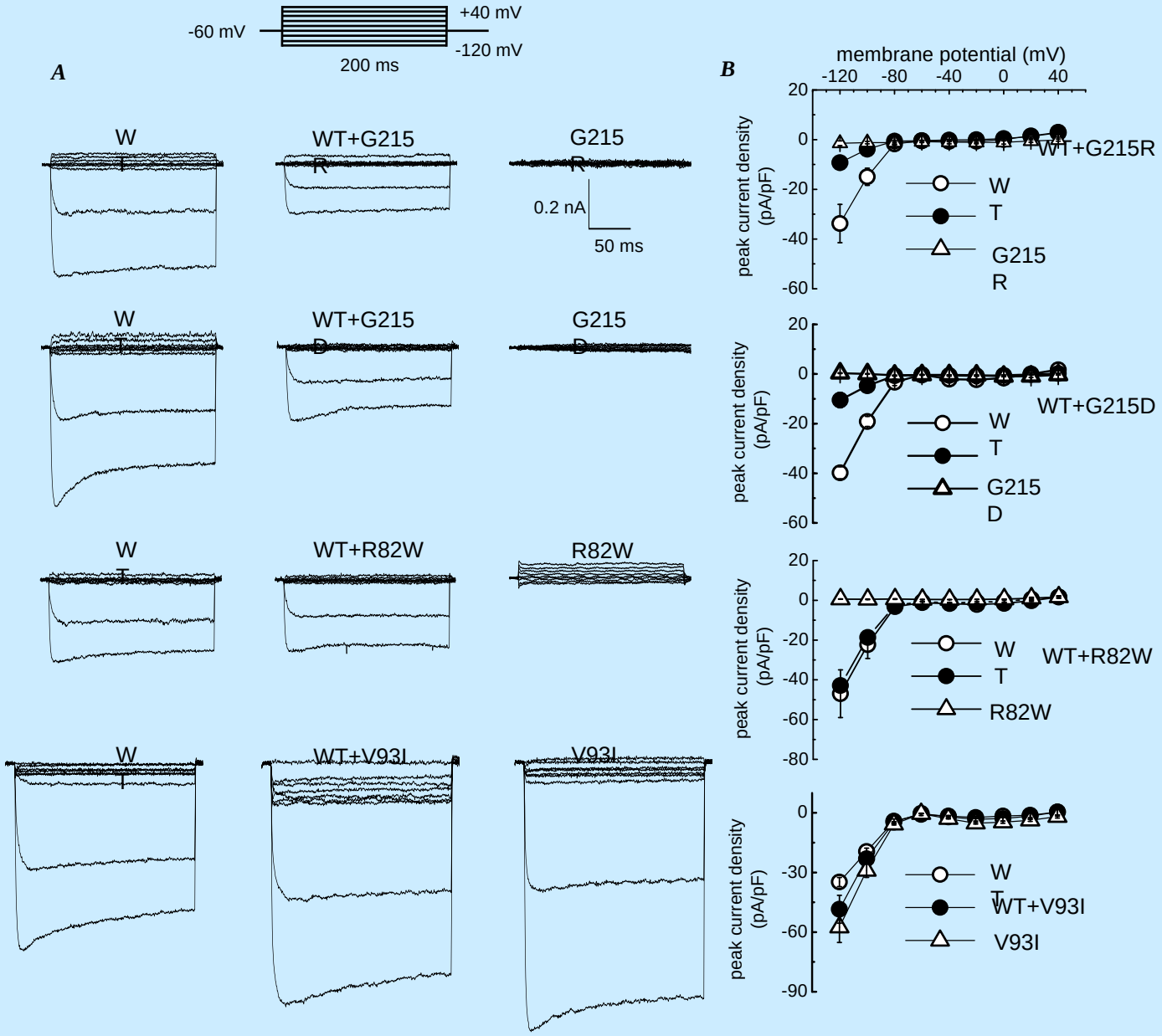
Inwardly rectifying K^+ channel Kir2.1



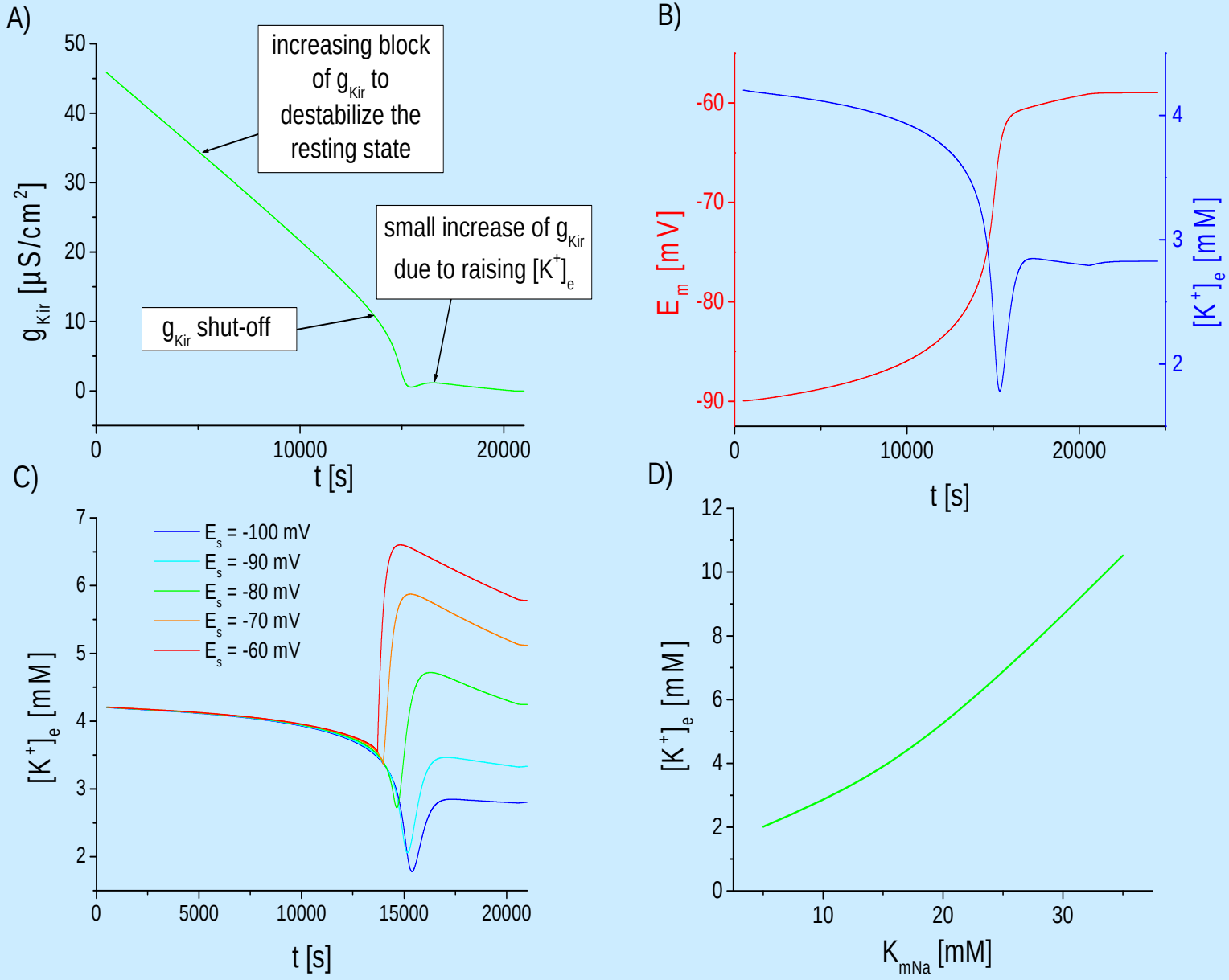
Expression of the normal (WT) and/or the mutated gene in COS cells



Currents through the mutant Kir2.1 channel

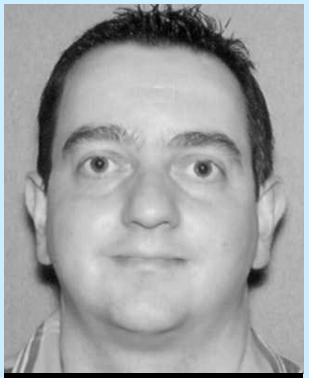


A,B: Depolarization and hypokalemia at reduced Kir2.1 function
C,D: Serum K^+ depends on individual slow Na^+ channel inactivation

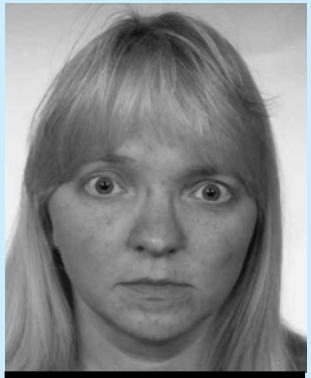


Reduced- and increased-function mutations are associated with different features

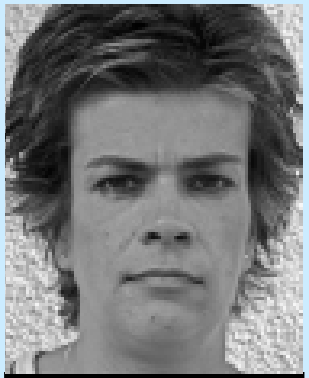
Hypertelorism



R82W

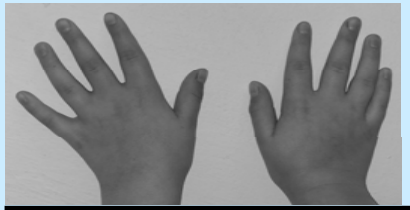


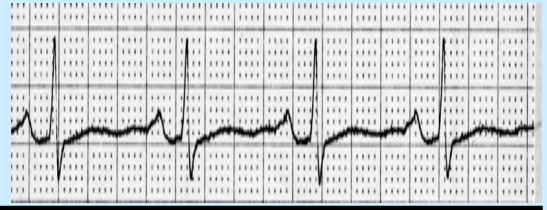
G215R



V93I

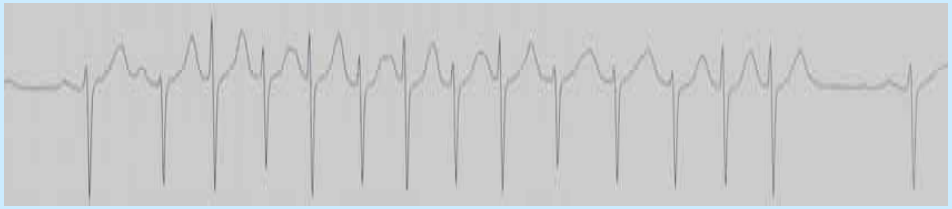
Hypotelorism





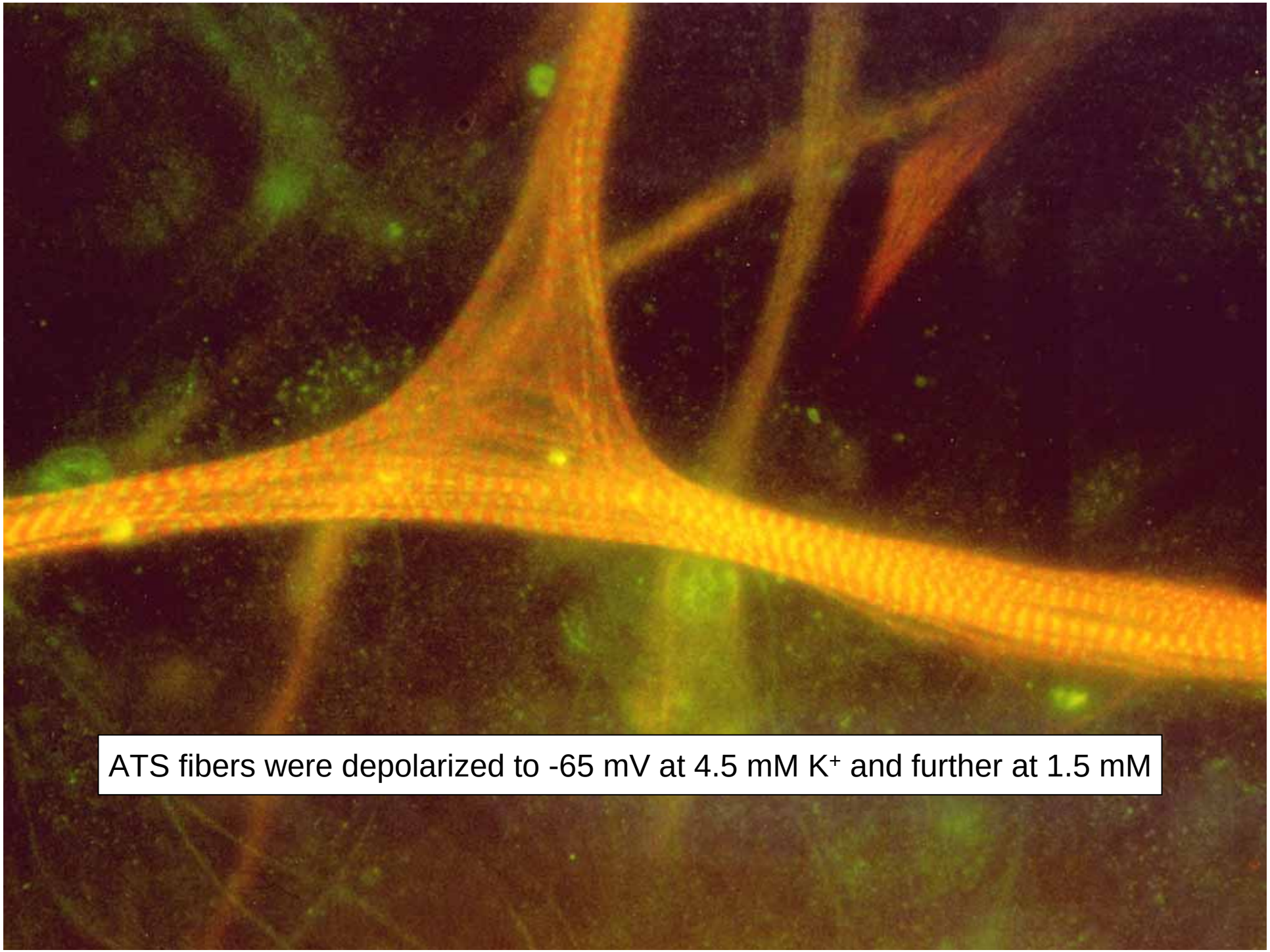
G215R

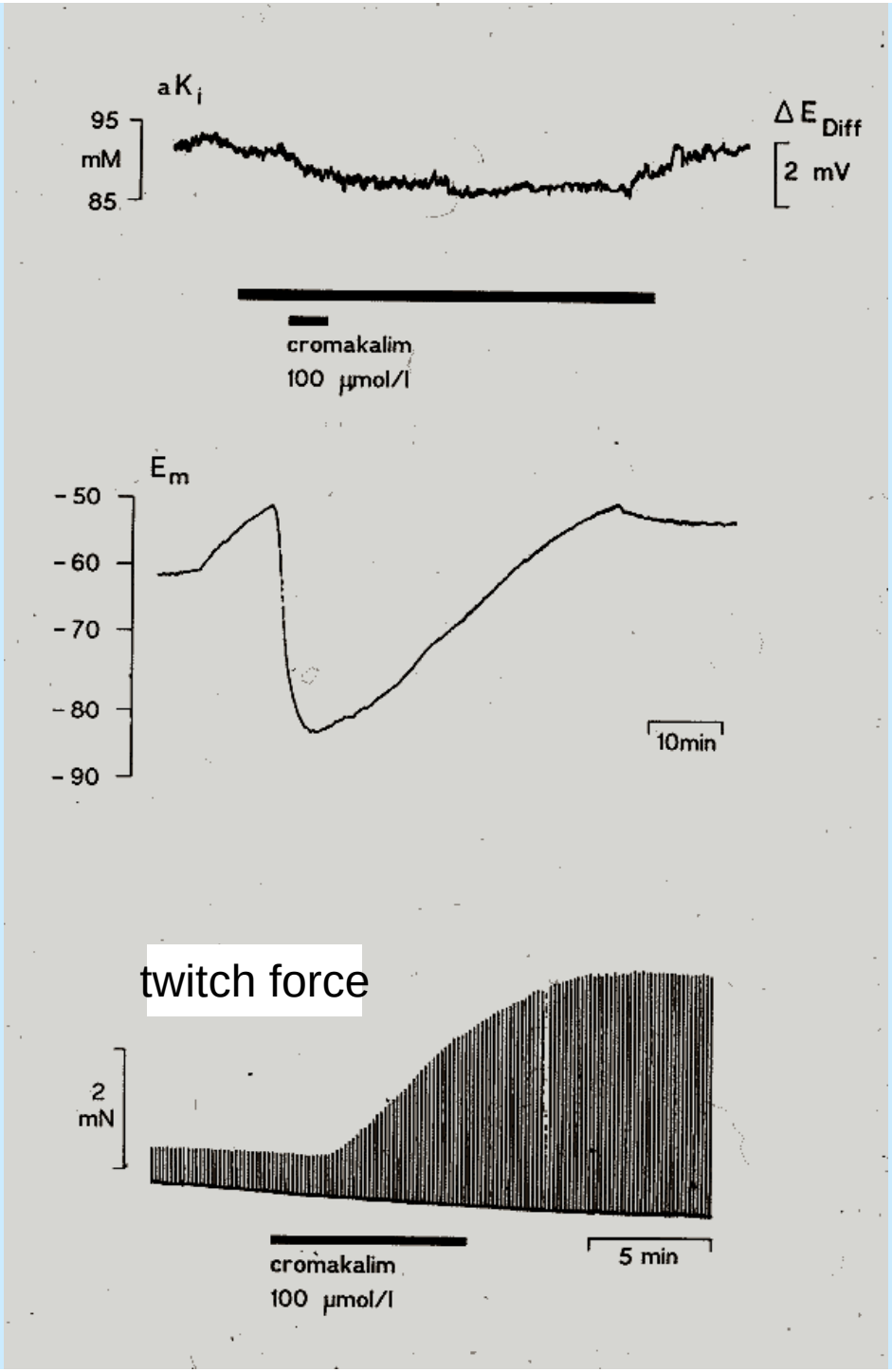
characteristic
TU morphology



V93I

AT


ATS fibers were depolarized to -65 mV at 4.5 mM K^+ and further at 1.5 mM


$a K_i$
95
mM
85
ΔE_{Diff}
2 mV
cromakalim
100 µmol/l
E_m
-50
-60
-70
-80
-90
10min
twitch force
2
mN
cromakalim
100 µmol/l
5 min

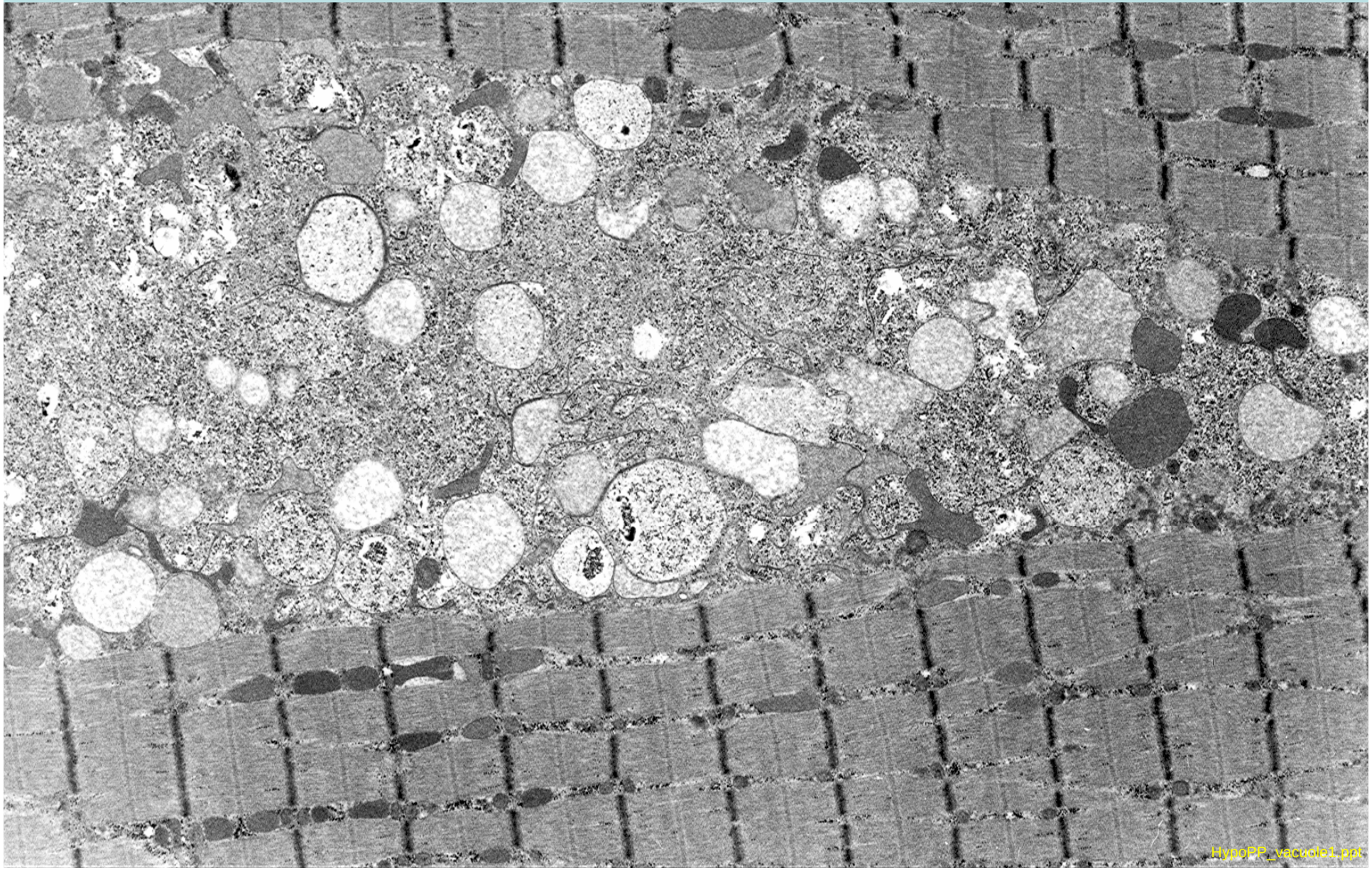
ATS patients: paralytic attacks

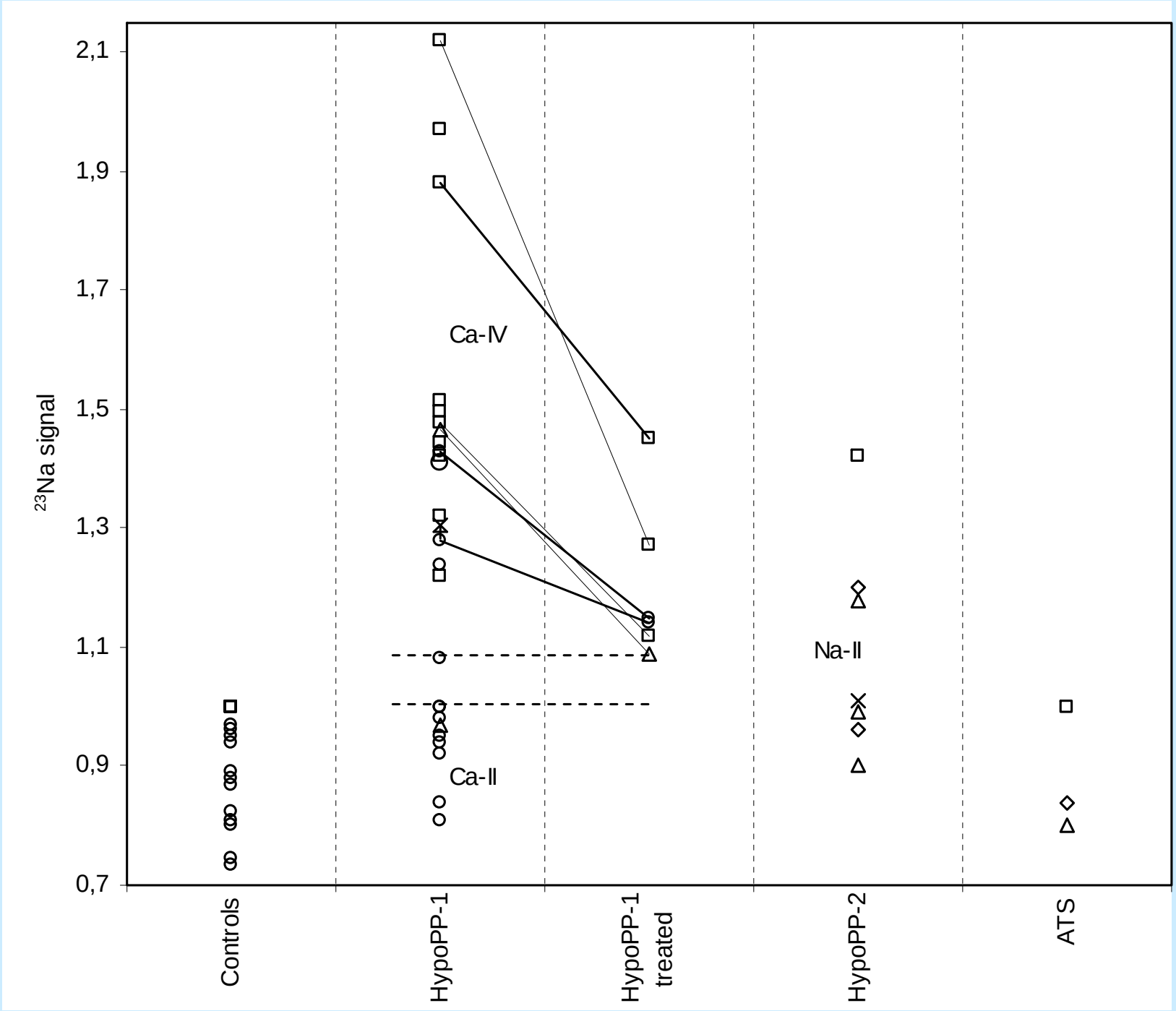
Kir2.1 muta-tions	Sex M;f	on-set	1st symptom	K^+/mM paralysis	PP type	Maxim. duration	chronic weakness	Muscle histology	Reaction to CAI
R67W	6;1	12	Para/Arrh	very low	HypoPP	Days	Yes (1/6)	Vacuoles	n.d.
D78G	0;1	8	Paralysis	low	HypoPP	Days	Yes (1/1)	Vacuoles	Beneficial
R82W	2;0	33	Para/Arrh	2.6	HypoPP	Days	No (1/1)	n.d.	n.d.
G215D	1;0	3	Paralysis	5.8	HyperPP	Days	Yes (1/1)	n.d.	No effect
G215R	0;2	9,5	Paralysis	2.4	HypoPP	Days	Yes (1/2)	Vacuoles	Worsening
R218W	2;4	8,3	Paralysis	5.7	HyperPP	Hours	No (6/6)	Vacuoles	Beneficial
R218Q	3;0	9,3	Para/Arrh	2.7	HypoPP	h/days	Yes (1/3)	Vacuoles	Severe side effects
V93I	1;1	30	Paralysis	1.9	HypoPP	weeks	No (1/1)	n.d.	n.d.

Cardiac features

Kir2.1 mutation	Type of arrhythmia	ECG QT_c	Effective therapy	Provoked by
R67W	PVC, bigeminus	< 440	Exercise, no effective drug	Stress, work, CAI
D78G	PVC	?	?	Hyperthyroidism
R82W	PVC	> 440	Digoxin	Hyperthyroidism
G215D	PVC, bigeminus	-	-	-
G215R	PVC, VT	> 440	-	Low-K, stress, work
R218W	PVC	< 440	Exercise, β-blocker, amioderone	Iodide
R218Q	PVC, VT, bigeminus	< 440	amiodarone	-
V93I	AT	< 440	-	-

Electrolyte and water dysequilibrium during paralytic attacks causes vacuolar myopathy




2,1
1,9
1,7
1,5
1,3
1,1
0,9
0,7
^{23}Na signal
Ca-Ⅳ
Ca-Ⅱ
Na-Ⅱ
Controls
HypoPP-1
HypoPP-1 treated
HypoPP-2
ATS

At rest

Therapy of ATS

Therapy of paralytic attacks:
Hypokalemic paralytic attacks as in HypoPP
Hyperkalemic paralytic attacks as in HyperPP
If type of attack is unknown: try potassium since ingestion-induced hyperkalemia is much less dangerous to the heart than hypokalemia!

Therapy of arrhythmia:
Na^+ channel blockers like propafenone (1st choice)
Imipramine according to old reports on HyperPP with arrhythmia
Amiodarone only in older patients (late side effects)
Pacemaker/defibrillator in drug-resistant ventricular tachycardia

Our experience: arrhythmias are improved by slight exercise but worsened by strenuous work