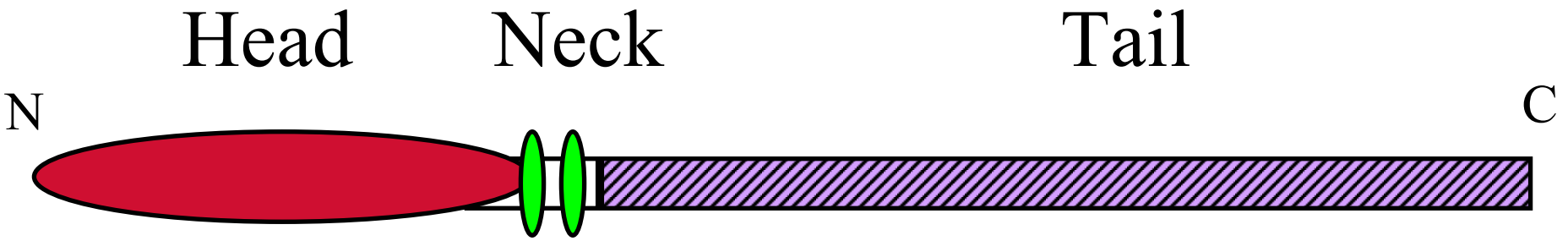
Conventional Myosin

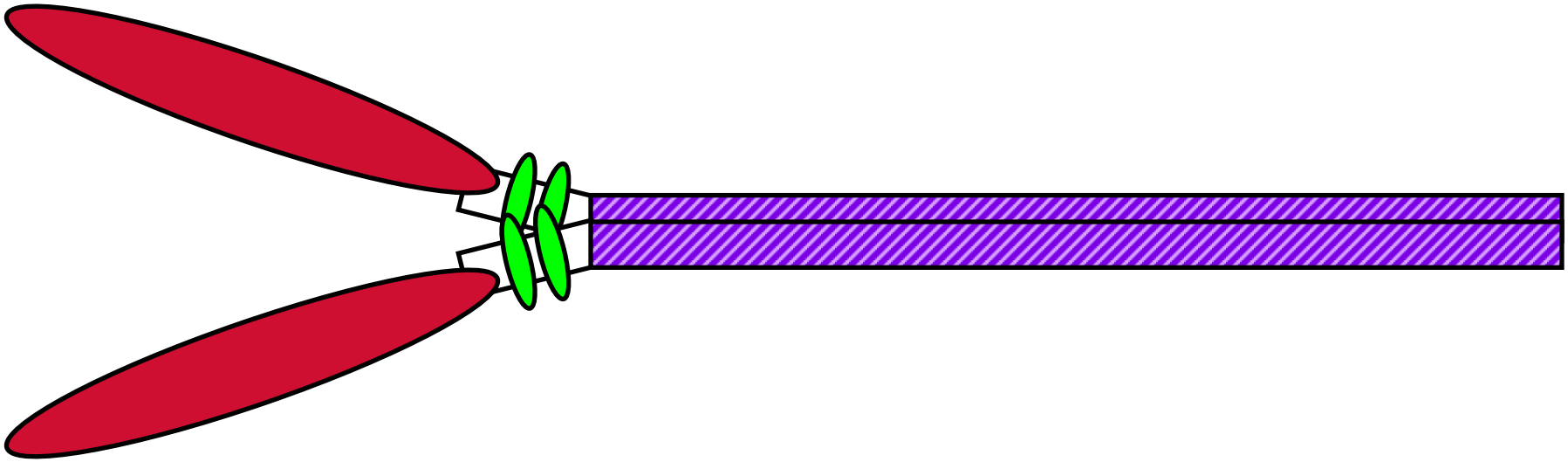


Motor domain
- actin binding
- ATP hydrolysis

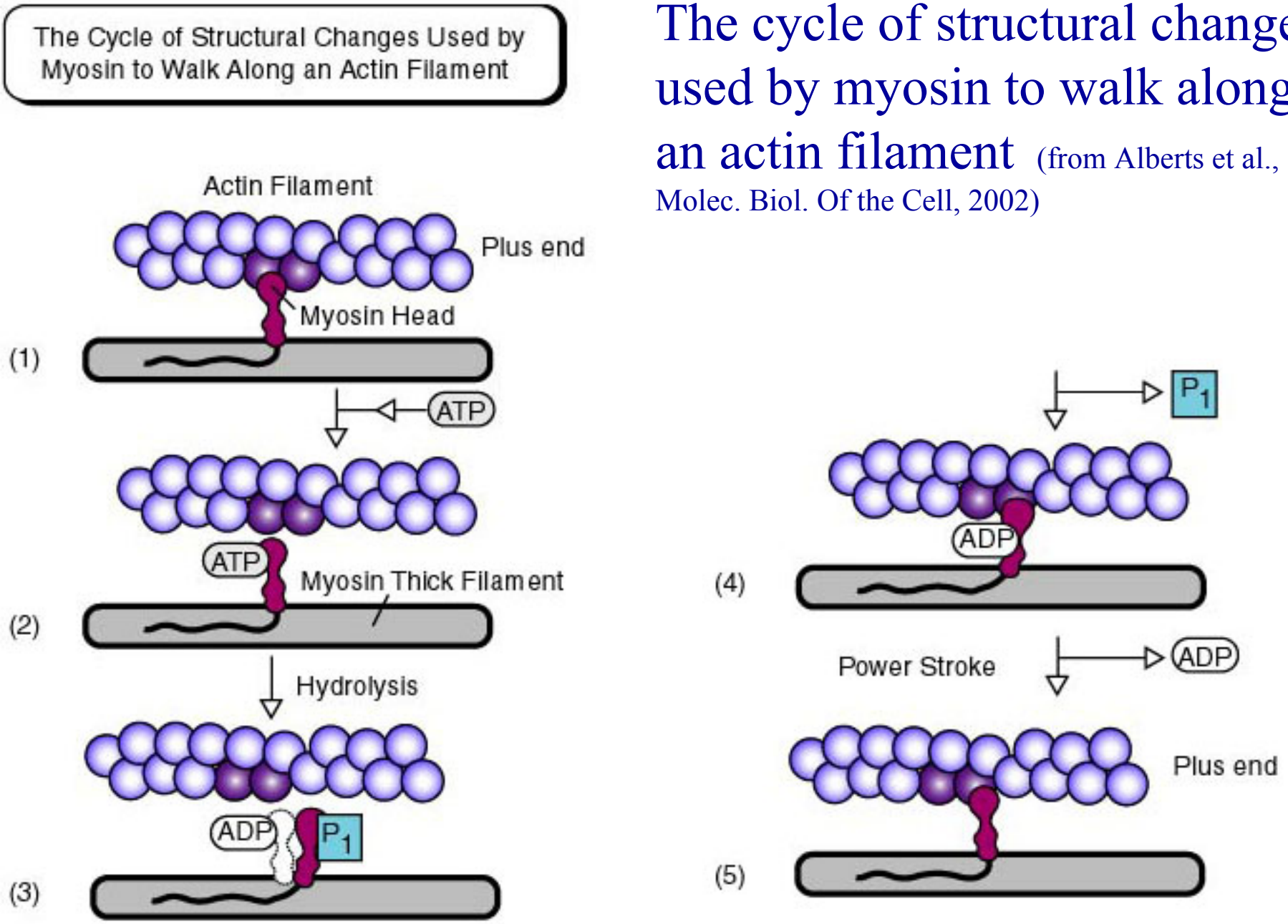
Colied-coil domain
- dimerization

Regulatory region (IQ)
- light chain binding

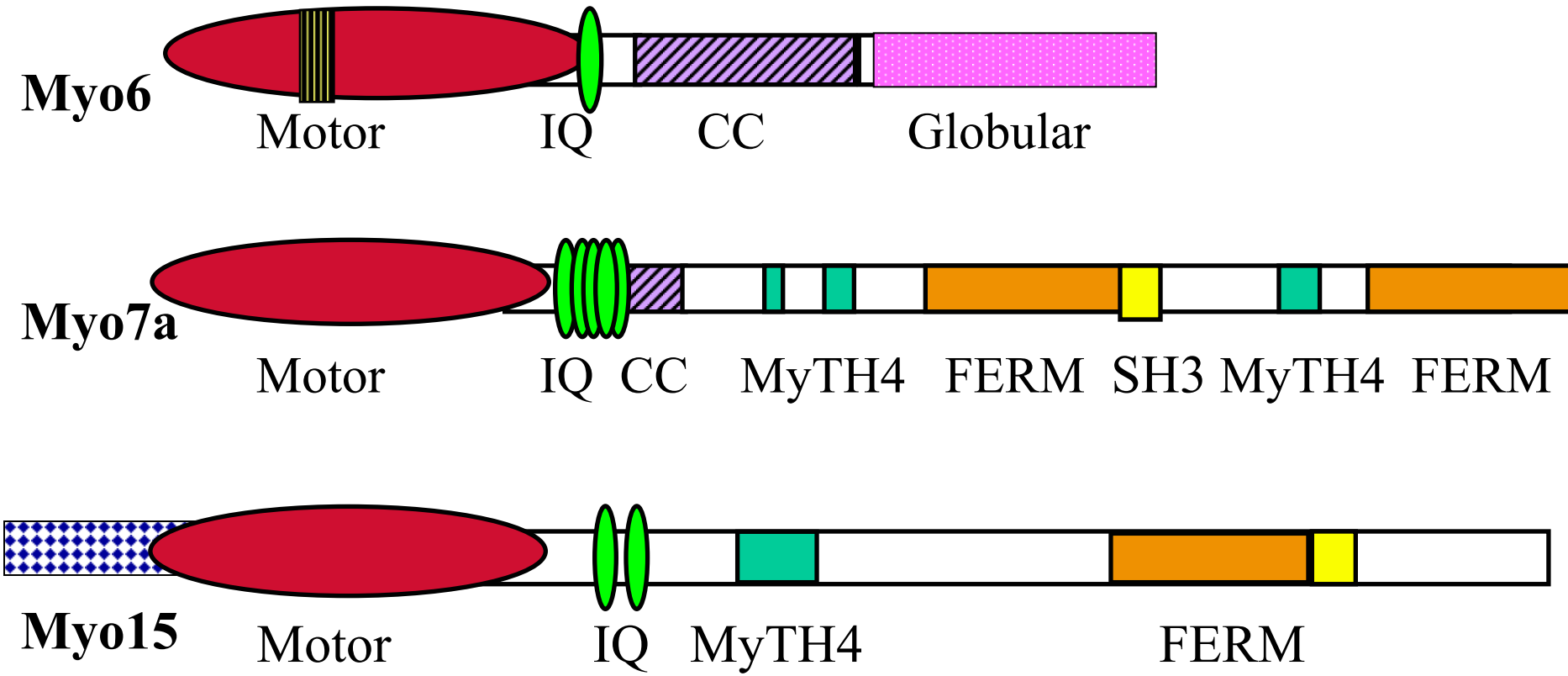
Myosin Dimer

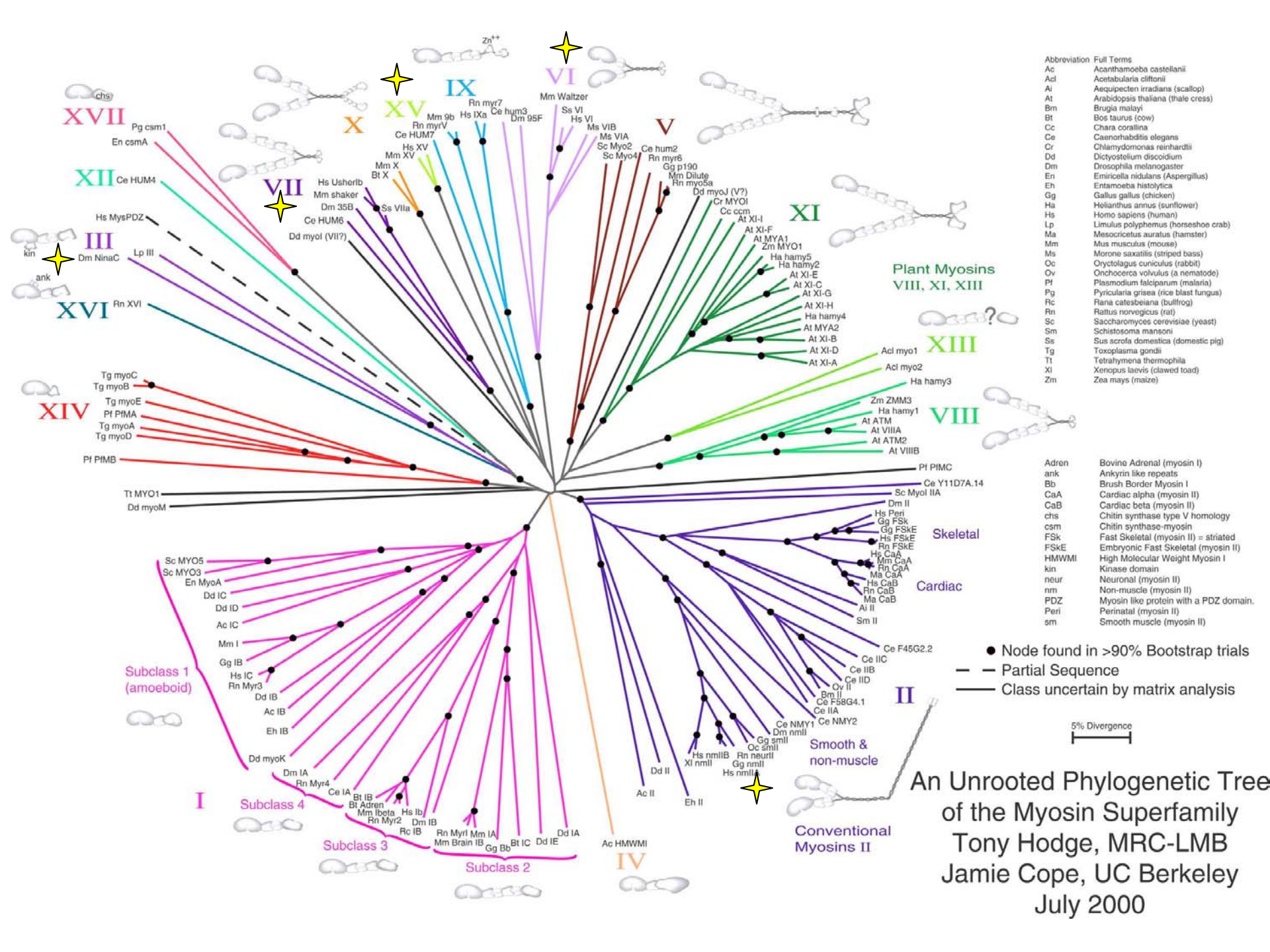


The cycle of structural changes used by myosin to walk along an actin filament (from Alberts et al., Molec. Biol. Of the Cell, 2002)



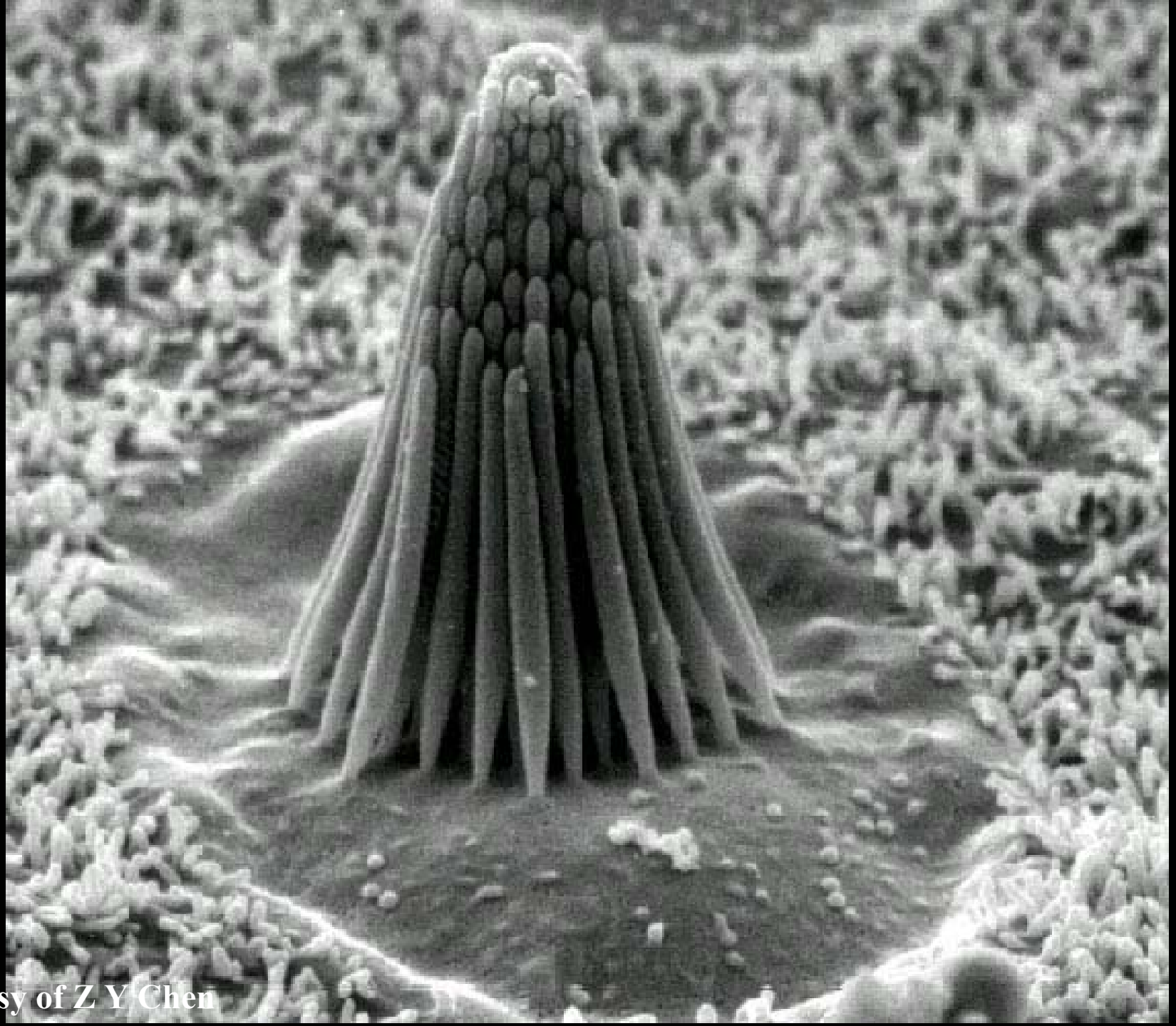
Myo6, Myo7a, Myo15



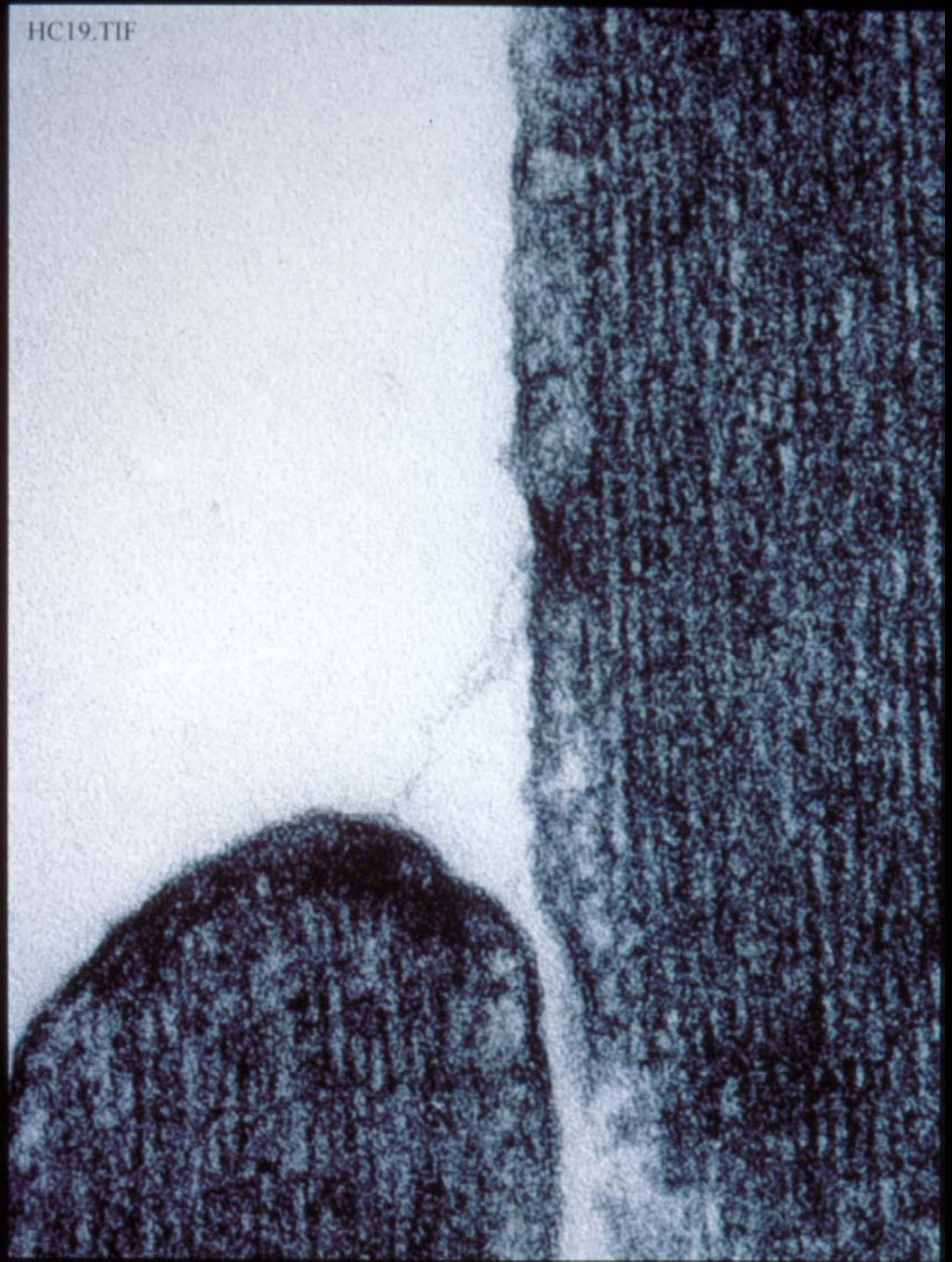

Zn++
chs
XVII
Pg csm1
En csmA
XII
Ce HUM4
III
Hs MysPDZ
kin
Dm NinaC
Lp III
ank
XVI
Rn XVI
XIV
Tg myoC
Tg myoB
Tg myoE
Pf PfMA
Tg myoA
Tg myoD
Pf PfMB
Tt MYO1
Dd myoM
Sc MYO5
Sc MYO3
En MyoA
Dd IC
Dd ID
Ac IC
Mm I
Gg IB
Hs IC
Rn Myr3
Dd IB
Ac IB
Eh IB
Dd myoK
Subclass 1
(amoeboid)
I
Dm IA
Rn Myr4
Ce IA
Bt IB
Bt Adren
Mm Ibeta
Hs Ib
Rn Myr2
Dm IB
Rc IB
Subclass 4
Rn MyrI
Mm Brain IB
Mm IA
Gg Bb
Bt IC
Dd IE
Dd IA
Subclass 3
Subclass 2
Ac HMWMI
IV
Ac II
Dd II
Eh II
Hs nmIIB
Xl nmII
Rn neurII
Gg nmII
Hs nmIIA
Ce NMY1
Dm nmII
Gg smII
Oc smII
Ce NMY2
Smooth &
non-muscle
Conventional
Myosins II
Ce F58G4.1
Ce IIA
Bm II
Ov II
Ce IID
Ce IIB
Ce IIC
Ce F45G2.2
II
Sm II
Ai II
Ma CaB
Rn CaB
Hs CaB
Ma CaA
Rn CaA
Mm CaA
Hs CaA
Rn FSkE
Hs FSkE
Gg FSkE
Gg FSk
Hs Peri
Dm II
Sc MyoI IIA
Ce Y11D7A.14
Pf PfMC
Skeletal
Cardiac
Acl myo1
Acl myo2
Ha hamy3
Zm ZMM3
Ha hamy1
At ATM
At VIIIA
At ATM2
At VIIIB
VIII
Plant Myosins
VIII, XI, XIII
XIII
?
Ha hamy5
Ha hamy2
At XI-E
At XI-C
At XI-G
At XI-H
Ha hamy4
At MYA2
At XI-B
At XI-D
At XI-A
At MYA1
Zm MYO1
At XI-I
At XI-F
Cr MYOI
Cc ccm
Dd myoJ (V?)
XI
Mm Dilute
Rn myo5a
Gg p190
Ce hum2
Rn myr6
Sc Myo2
Sc Myo4
Ms VIA
Ms VIB
Ss VI
Hs VI
Mm Waltzer
V
VI
Rn myr7
Mm 9b
Hs IXa
Ce hum3
Dm 95F
IX
Rn myrV
Ce HUM7
Hs XV
Mm XV
Mm X
Bt X
XV
X
Hs Usherlb
Mm shaker
Dm 35B
Ss VIIa
Ce HUM6
Dd myoI (VII?)
VII
Lp III
Tg myoC
Tg myoB
Tg myoE
Pf PfMA
Tg myoA
Tg myoD
Pf PfMB
Tt MYO1
Dd myoM
Sc MYO5
Sc MYO3
En MyoA
Dd IC
Dd ID
Ac IC
Mm I
Gg IB
Hs IC
Rn Myr3
Dd IB
Ac IB
Eh IB
Dd myoK
Dm IA
Rn Myr4
Ce IA
Bt IB
Bt Adren
Mm Ibeta
Hs Ib
Rn Myr2
Dm IB
Rc IB
Rn MyrI
Mm Brain IB
Mm IA
Gg Bb
Bt IC
Dd IE
Dd IA
Ac HMWMI
Ac II
Dd II
Eh II
Hs nmIIB
Xl nmII
Rn neurII
Gg nmII
Hs nmIIA
Ce NMY1
Dm nmII
Gg smII
Oc smII
Ce NMY2
Ce F58G4.1
Ce IIA
Bm II
Ov II
Ce IID
Ce IIB
Ce IIC
Ce F45G2.2
Sm II
Ai II
Ma CaB
Rn CaB
Hs CaB
Ma CaA
Rn CaA
Mm CaA
Hs CaA
Rn FSkE
Hs FSkE
Gg FSkE
Gg FSk
Hs Peri
Dm II
Sc MyoI IIA
Ce Y11D7A.14
Pf PfMC
Acl myo1
Acl myo2
Ha hamy3
Zm ZMM3
Ha hamy1
At ATM
At VIIIA
At ATM2
At VIIIB
Ha hamy5
Ha hamy2
At XI-E
At XI-C
At XI-G
At XI-H
Ha hamy4
At MYA2
At XI-B
At XI-D
At XI-A
At MYA1
Zm MYO1
At XI-I
At XI-F
Cr MYOI
Cc ccm
Dd myoJ (V?)
Mm Dilute
Rn myo5a
Gg p190
Ce hum2
Rn myr6
Sc Myo2
Sc Myo4
Ms VIA
Ms VIB
Ss VI
Hs VI
Mm Waltzer
Rn myr7
Mm 9b
Hs IXa
Ce hum3
Dm 95F
Rn myrV
Ce HUM7
Hs XV
Mm XV
Mm X
Bt X
Hs Usherlb
Mm shaker
Dm 35B
Ss VIIa
Ce HUM6
Dd myoI (VII?)
Hs MysPDZ
Dm NinaC
Lp III
Rn XVI
Pg csm1
En csmA
Ce HUM4
Abbreviation Full Terms
Ac Acanthamoeba castellanii
Acl Acetabularia cliftonii
Ai Aequipecten irradians (scallop)
At Arabidopsis thaliana (thale cress)
Bm Brugia malayi
Bt Bos taurus (cow)
Cc Chara corallina
Ce Caenorhabditis elegans
Cr Chlamydomonas reinhardtii
Dd Dictyostelium discoidium
Dm Drosophila melanogaster
En Emericella nidulans (Aspergillus)
Eh Entamoeba histolytica
Gg Gallus gallus (chicken)
Ha Helianthus annus (sunflower)
Hs Homo sapiens (human)
Lp Limulus polyphemus (horseshoe crab)
Ma Mesocricetus auratus (hamster)
Mm Mus musculus (mouse)
Ms Morone saxatilis (striped bass)
Oc Oryctolagus cuniculus (rabbit)
Ov Onchocerca volvulus (a nematode)
Pf Plasmodium falciparum (malaria)
Pg Pyricularia grisea (rice blast fungus)
Rc Rana catesbeiana (bullfrog)
Rn Rattus norvegicus (rat)
Sc Saccharomyces cerevisiae (yeast)
Sm Schistosoma mansoni
Ss Sus scrofa domestica (domestic pig)
Tg Toxoplasma gondii
Tt Tetrahymena thermophila
Xl Xenopus laevis (clawed toad)
Zm Zea mays (maize)
Adren Bovine Adrenal (myosin I)
ank Ankyrin like repeats
Bb Brush Border Myosin I
CaA Cardiac alpha (myosin II)
CaB Cardiac beta (myosin II)
chs Chitin synthase type V homology
csm Chitin synthase-myosin
FSk Fast Skeletal (myosin II) = striated
FSkE Embryonic Fast Skeletal (myosin II)
HMWMI High Molecular Weight Myosin I
kin Kinase domain
neur Neuronal (myosin II)
nm Non-muscle (myosin II)
PDZ Myosin like protein with a PDZ domain.
Peri Perinatal (myosin II)
sm Smooth muscle (myosin II)
● Node found in >90% Bootstrap trials
– – Partial Sequence
—— Class uncertain by matrix analysis
5% Divergence
An Unrooted Phylogenetic Tree
of the Myosin Superfamily
Tony Hodge, MRC-LMB
Jamie Cope, UC Berkeley
July 2000

Myosins in the inner ear

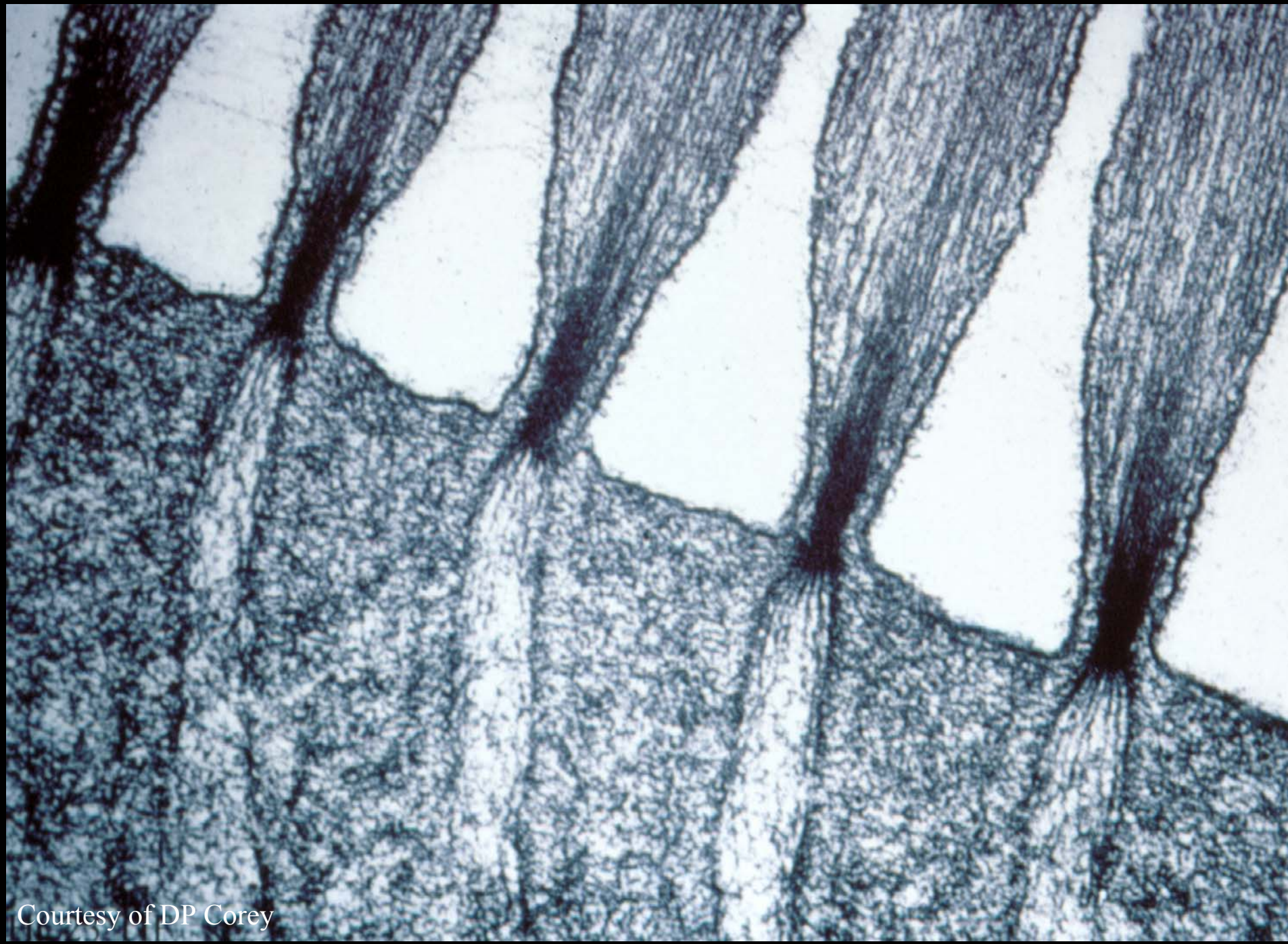
Gene	Mouse mutant	Human disease	Hair cell defects
MYO1β			
MYO3A		DFNB30	
MYO6	Snell's waltzer	DFNA22	Fused stereocillia
MYO7A	shaker 1	Usher 1B, DFNA11/B2	Splayed sterocillia
MYH9		DFNA17	
MYO15	shaker 2	DFNB3	Short sterocillia, actin rods



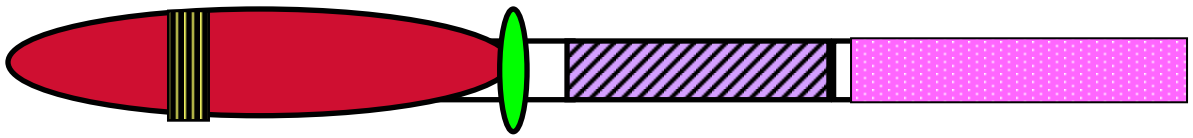
Courtesy of Z Y Chen



Courtesy of DP Corey


Courtesy of DP Corey

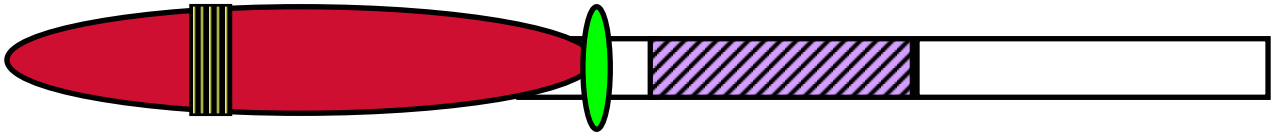
Myosin VI



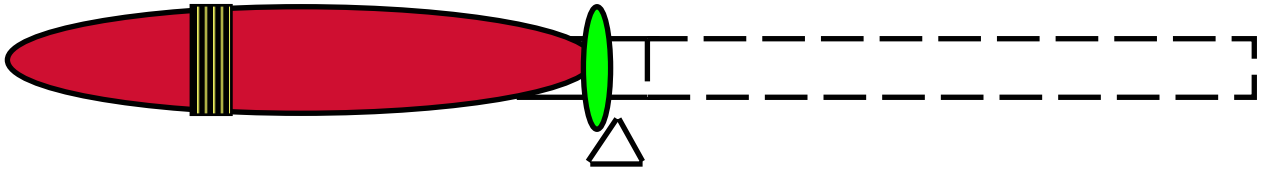
Motor IQ CC Globular

Mutations in Myosin VI Producing Deafness

Myosin VI



Myosin VI Snell's Waltzer

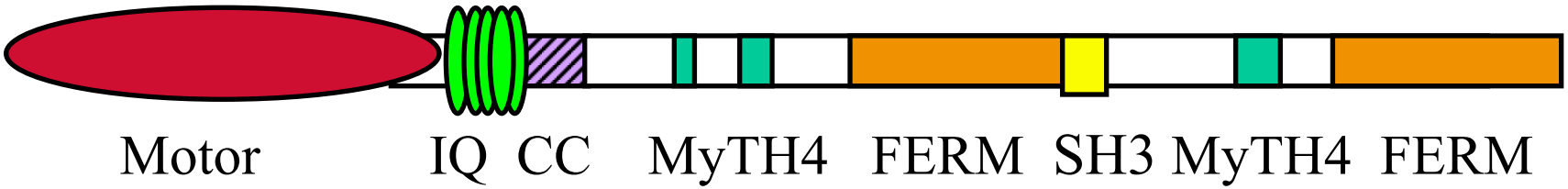


130 bp deletion

Model for stereocilia fusion in the absence of *MYO6* in the *snell's waltzer* mouse.

Self et al., Dev. Biol., 1999, 214;331

Myosin VIIa



Myosin VIIa and Human Deafness

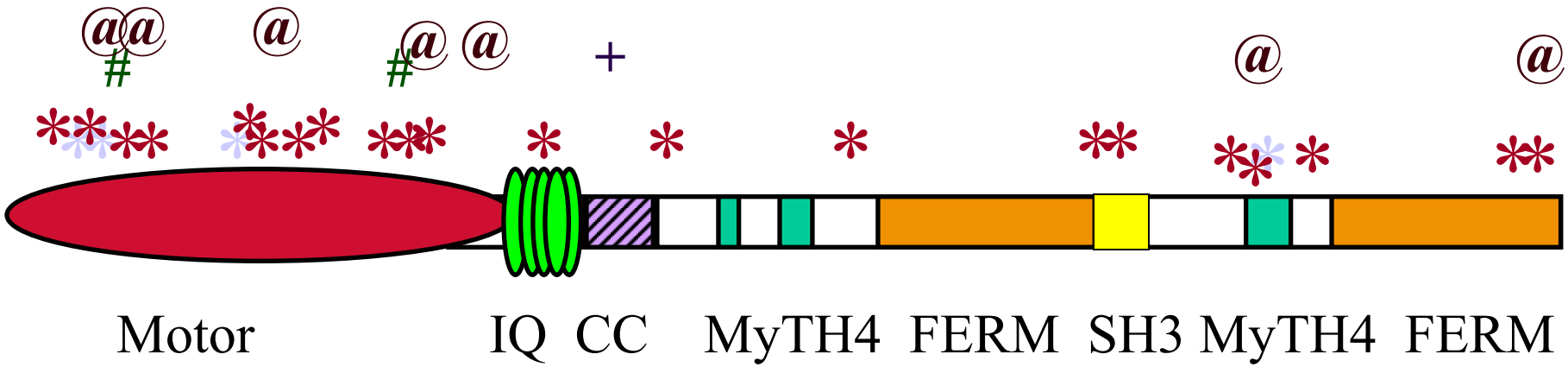
	Hearing Loss	Onset	Other Features	Vestibular Function
USH1B	profound	congenital	retinitis pigmentosa	absent
DFNB2	profound	congenital	none	variable
DFNA11	moderate	post-lingual	none	variable

The Usher syndromes

- ~50% of the deaf blind population has Usher syndrome
- There are at least 11 Usher syndrome loci; 6 genes identified to date
- Type 1: profound congenital hearing loss, vestibular areflexia, early onset vision loss
- Type 2: congenital sloping hearing loss, normal vestibular, 1st or 2nd decade vision loss
- Type 3: progressive hearing loss, varible vestibular and vision defects

Mutations in Myosin VIIa Producing Deafness

Usher 1B mutations *
DFNB2 mutations #
DFNA11 mutations +
shaker-1 mutations @

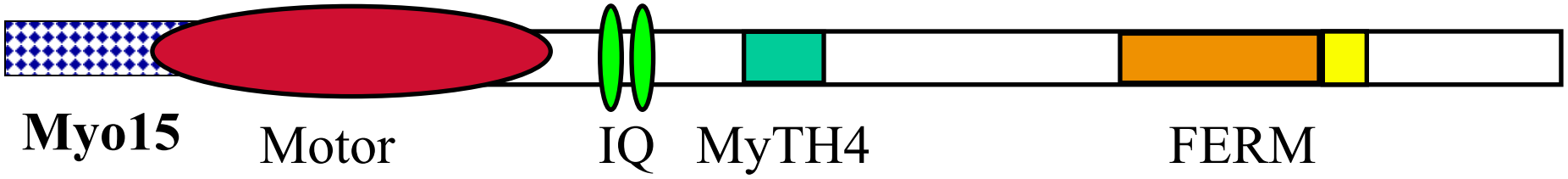


Myosin VIIa Tissue Expression

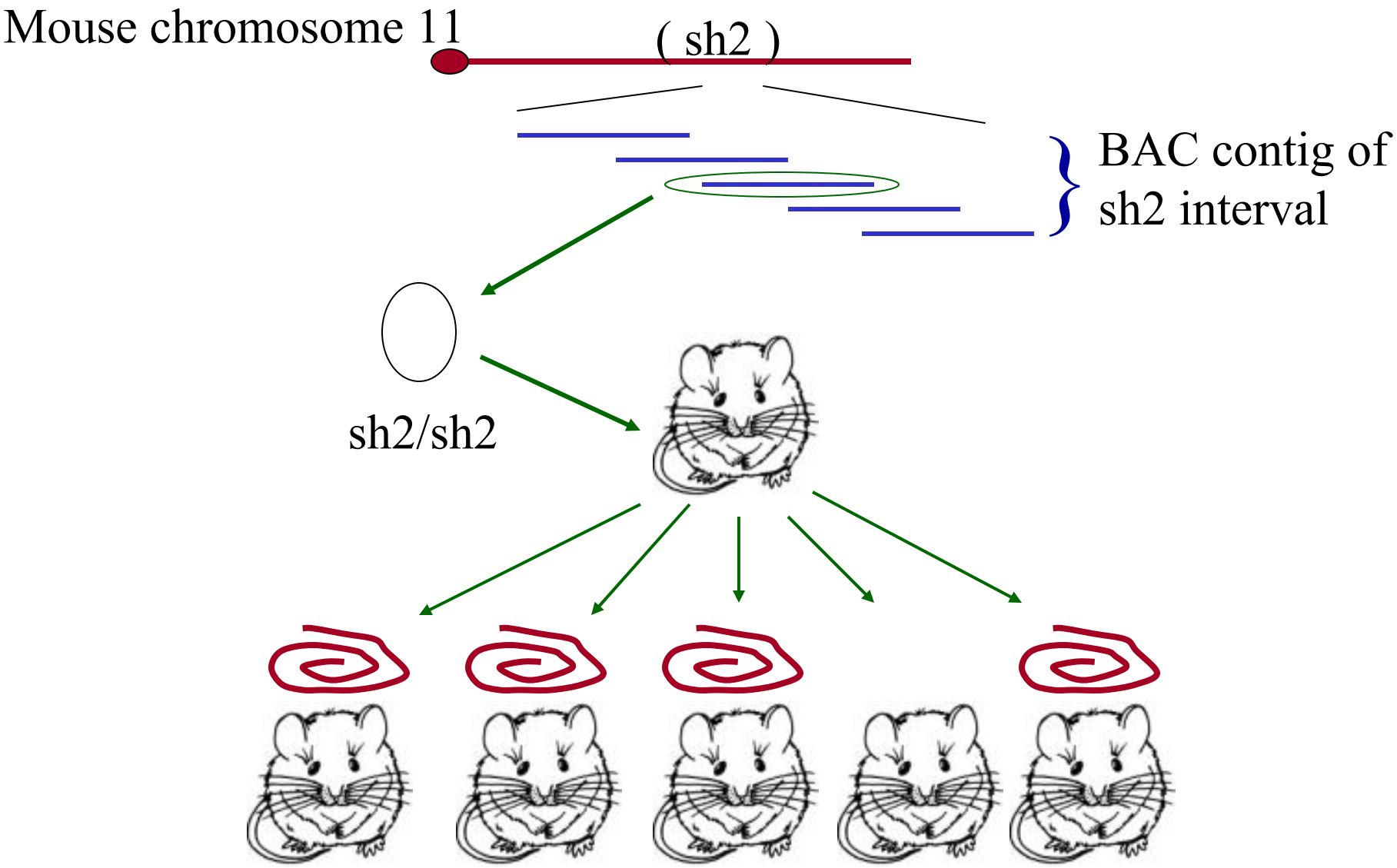
Myosin VIIa is exclusively expressed in:

- retina
  - retinal pigment epithelium — **Human** **Mouse**
  - photoreceptor cells — **Human**
- lung
- kidney
- testis
- inner ear
  - inner hair cells — **Human** **Mouse**
  - outer hair cells — **Human** **Mouse**

Myosin 15



Functional cloning to rescue the *shaker 2* phenotype



Pedigrees and MYO15 allele segregation from 3 DFNB3 families

See Wang et al., Science, 1998, 280:1447

DNA sequence of MYO15 from 3 DFNB3 families

See Wang et al., Science, 1998, 280:1447

Stereocilia of *shaker 2* mouse

See Probst et al., Science, 1998, 280:1444

Progressive hearing loss in DFNB30

See Walsh et al., PNAS, 2002, 99;7518

MYO 3A staining in mouse inner and outer hair cells

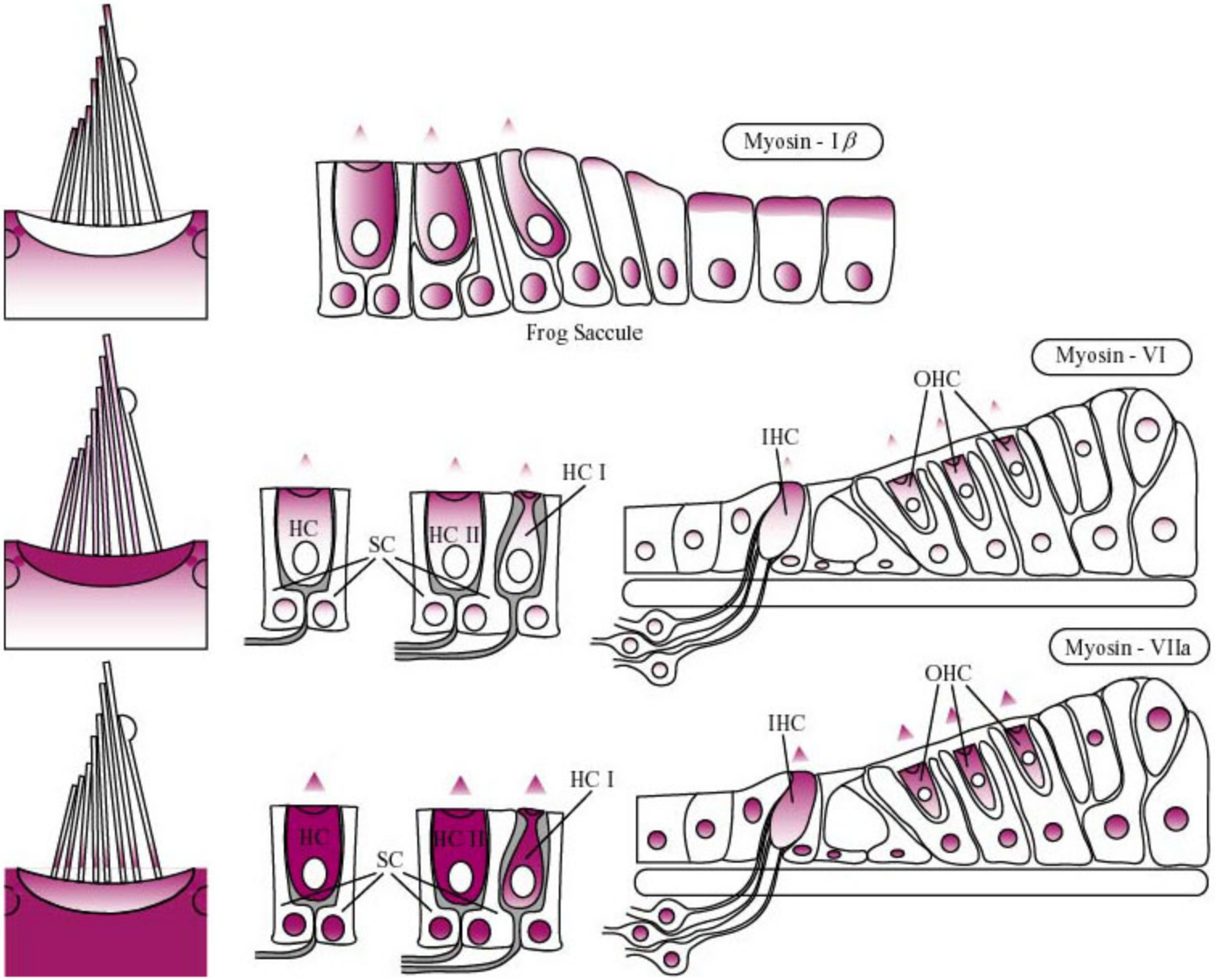
See Walsh et al., PNAS, 2002, 99;7518

DFNA17 kindred and sequence of MYH9

See Lalwani et al., Am. J. Hum. Genet., 2000, 67:1121

MYH9 expression in rat cochlea

See Lalwani et al., Am. J. Hum. Genet., 2000, 67:1121



Hasson et al., J. Cell Biol., 1997, 137;1287

Additional Readings:

Rayment et al. (1993) Science **261**: 50-58

Hasson et al., J. Cell Biol., 1997, 137;1287

Self et al., Dev. Biol., 1999, 214;331

Hasson et al., J. Cell Biol., 1997, 137; 1300, 1287, and 1287

Holme and Steel, Trends in Molec. Med. 7(3) 1 March 2001, Page 138

Probst et al., Science, 1998, 280:1444