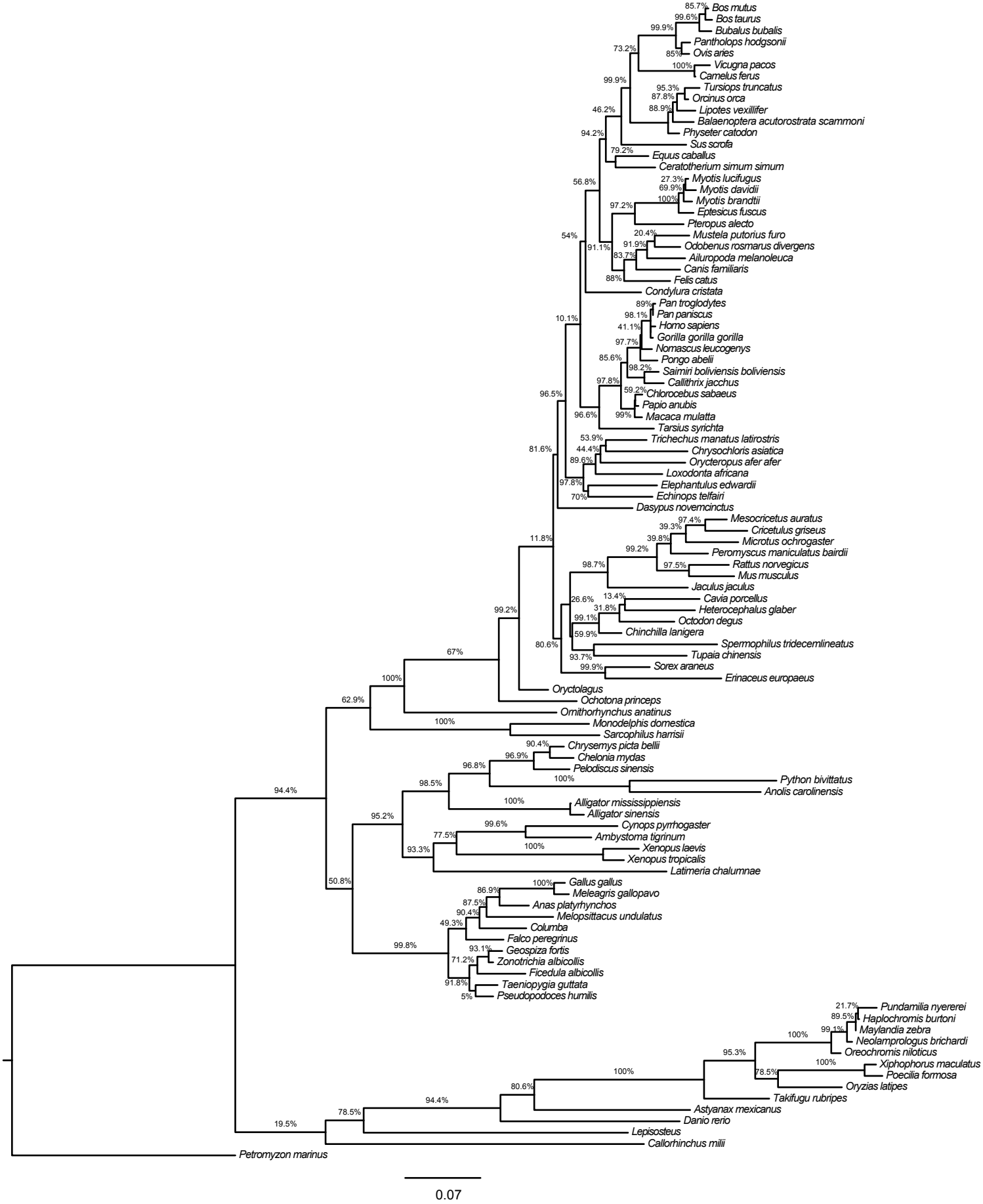
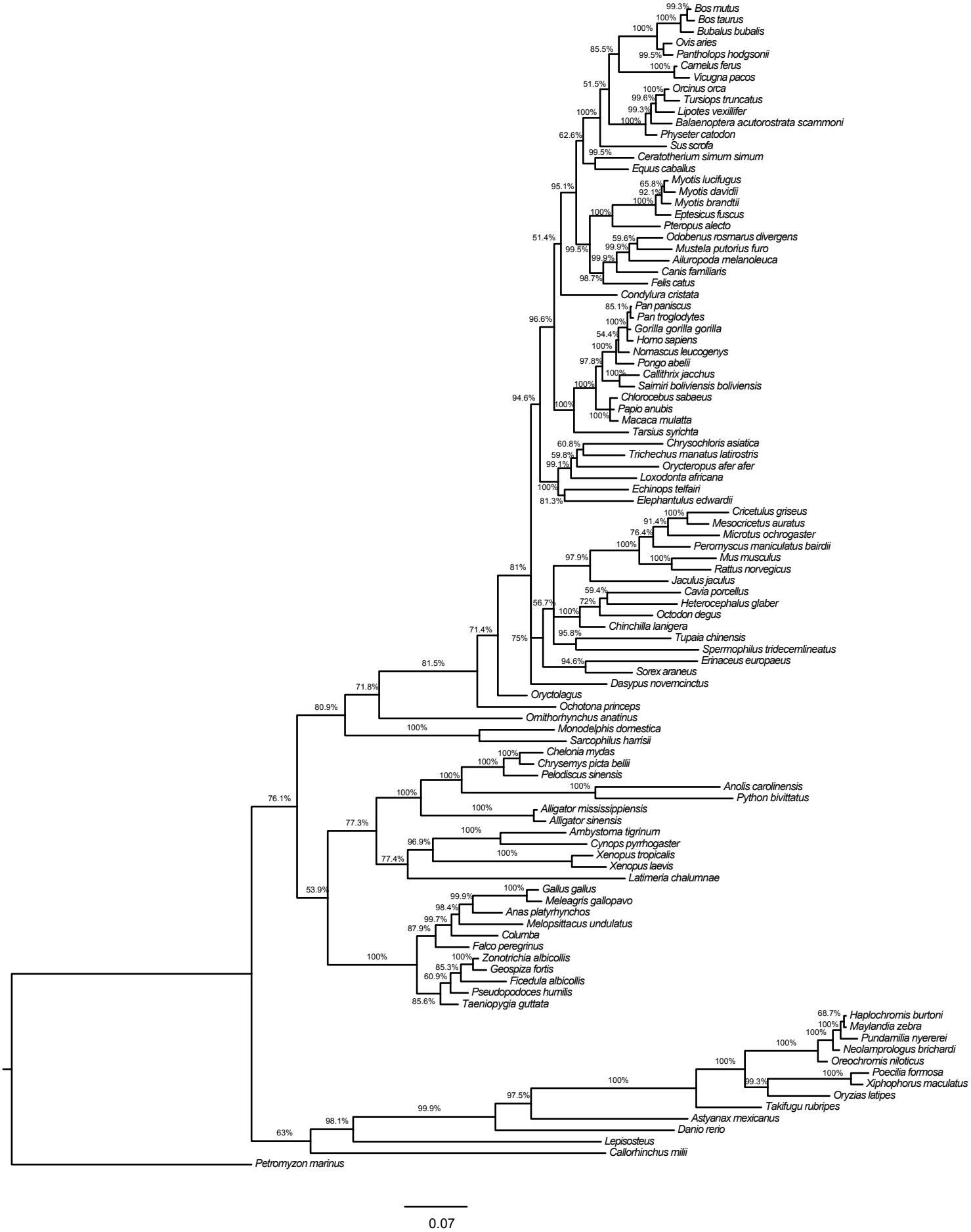
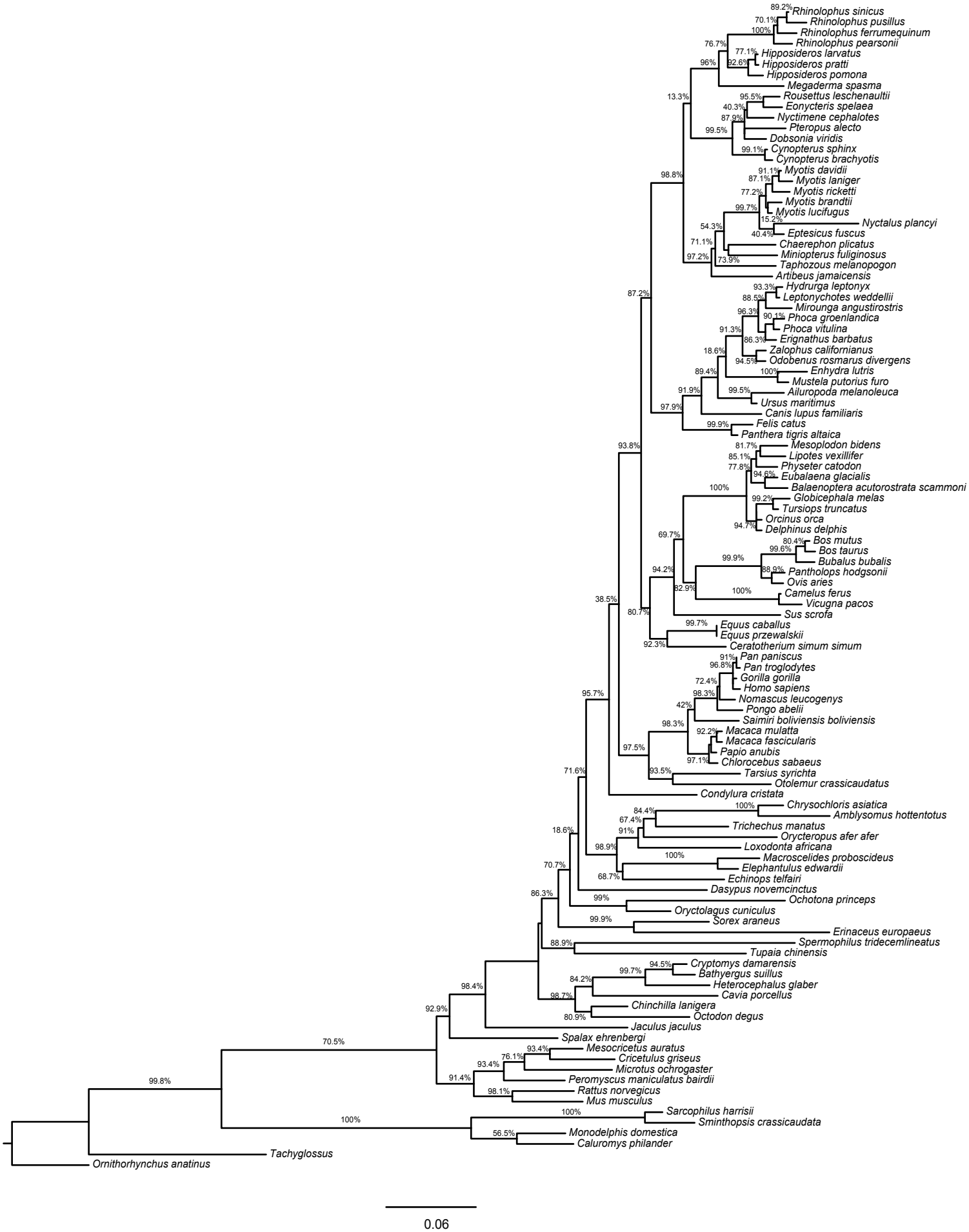


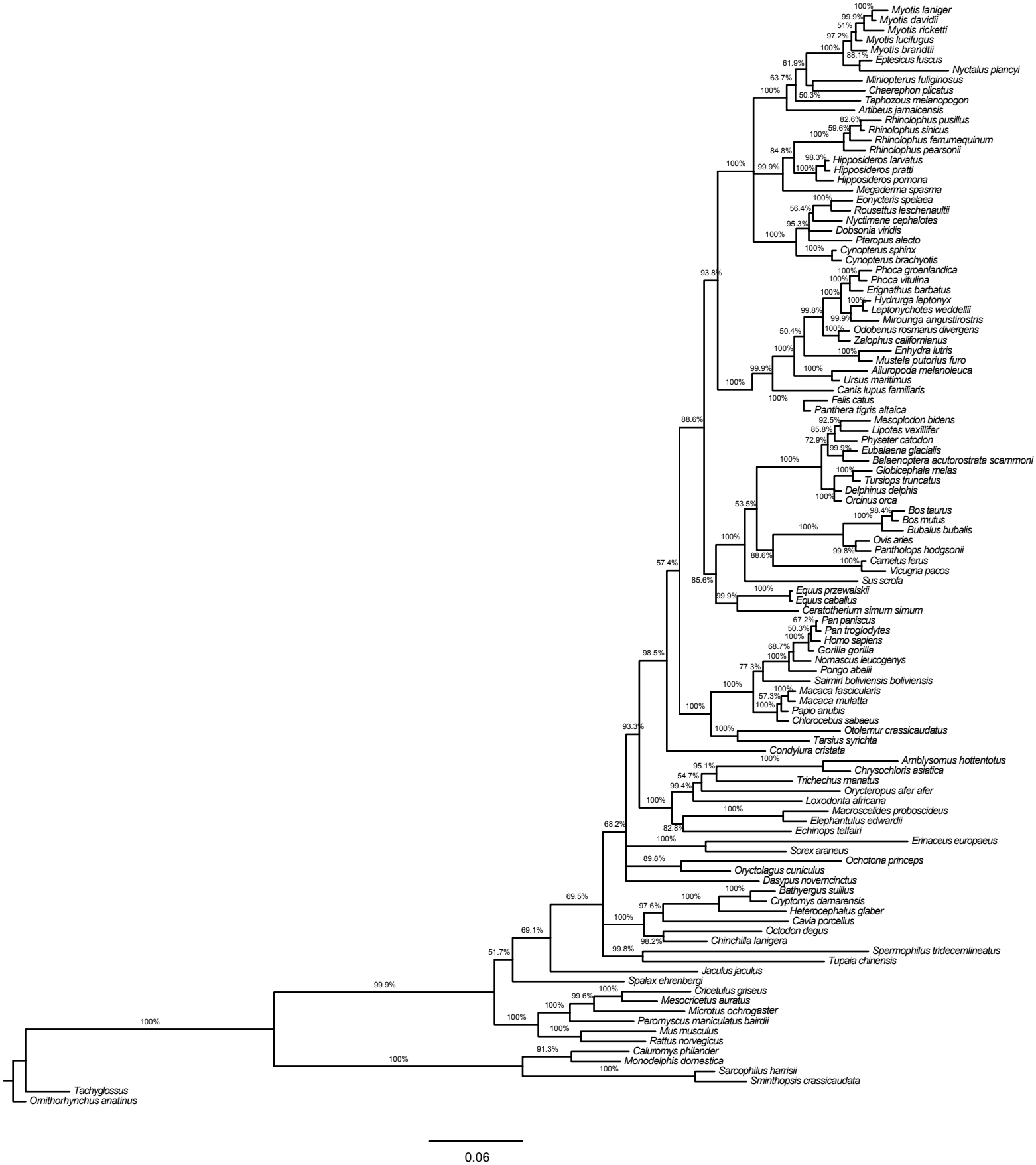

**Supplementary Figure S1.** Vertebrate RHO gene tree estimated by maximum likelihood (PHYML). Numbers at the nodes are aLRT support values.




**Supplementary Figure S2.** Vertebrate RHO gene tree estimated by Bayesian inference (MrBayes). Numbers at the nodes are posterior probabilities.



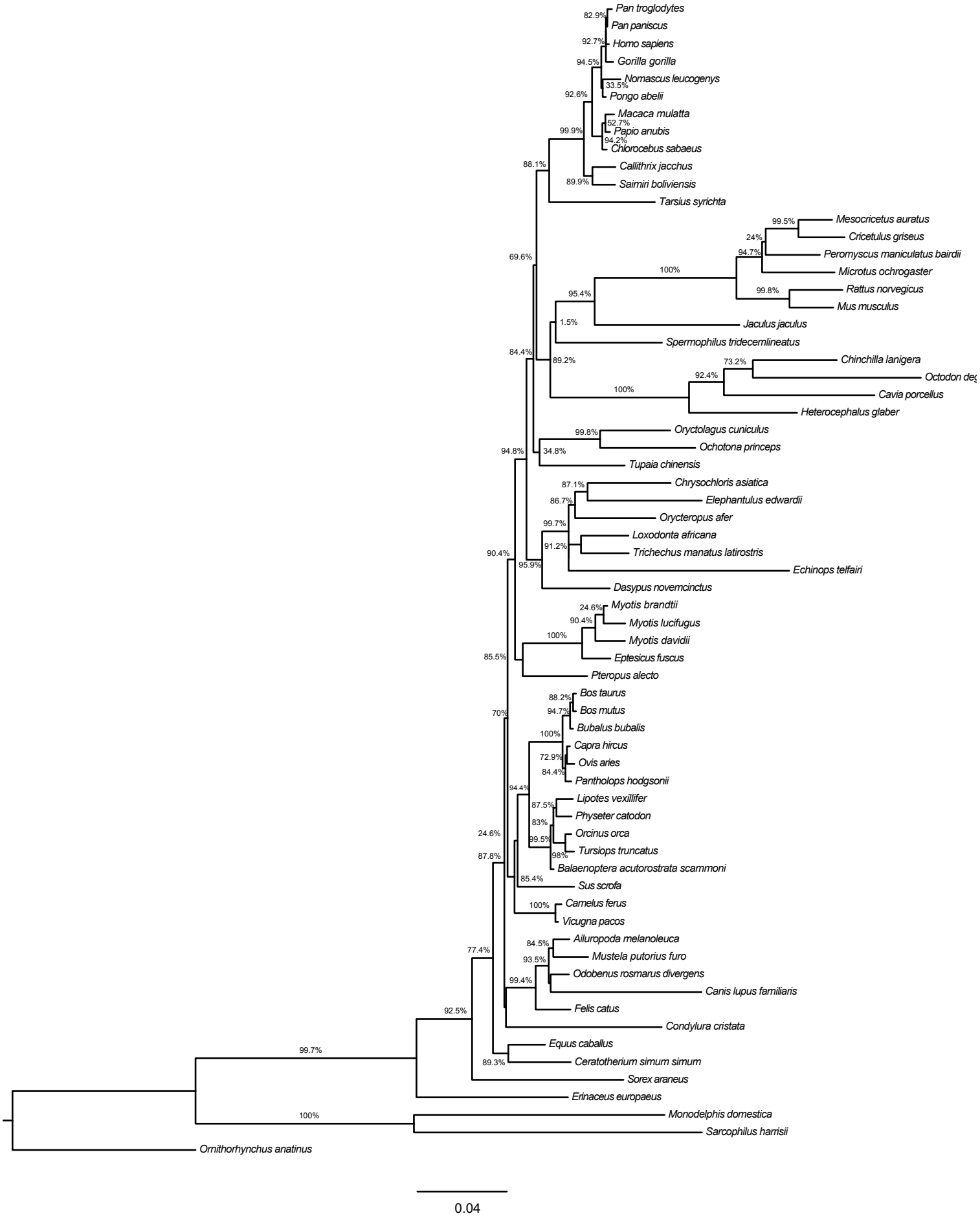

**Supplementary Figure S3.** Mammalian RHO gene tree estimated by maximum likelihood (PHYML). Numbers at the nodes are aLRT support values.



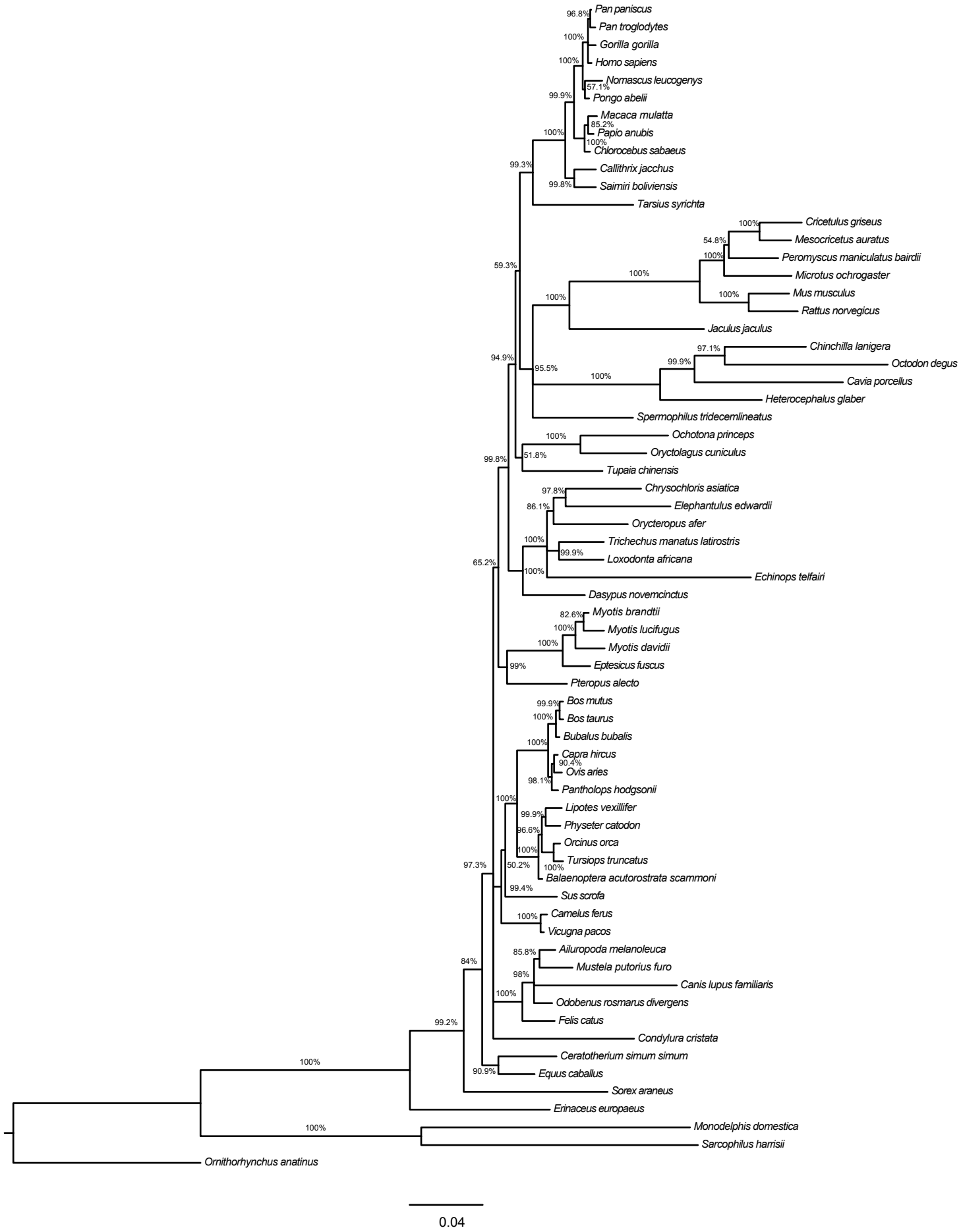

**Supplementary Figure S4.** Mammalian RHO gene tree estimated by Bayesian inference (MrBayes). Numbers at the nodes are posterior probabilities.


**Supplementary Figure S5.** Vertebrate RPE65 gene tree estimated by maximum likelihood (PHYML). Numbers at the nodes are aLRT support values.


**Supplementary Figure S6.** Vertebrate RPE65 gene tree estimated by Bayesian inference (MrBayes). Numbers at the nodes are posterior probabilities.




**Supplementary Figure S7.** Mammalian RPE65 gene tree estimated by maximum likelihood (PHYML). Numbers at the nodes are aLRT support values.




**Supplementary Figure S8.** Mammalian RPE65 gene tree estimated by Bayesian inference (MrBayes). Numbers at the nodes are posterior probabilities.

**Table S1. RHO and RPE65 Accession numbers**

| Species Name | Accession Number |
|---|---|
| **Vertebrate RHO data set:** | |
| *Ailuropoda melanoleuca* | XM_002921249.2 |
| *Alligator mississippiensis* | NM_001287282.1 |
| *Alligator sinensis* | XM_006039400.1 |
| *Ambystoma tigrinum* | U36574.1 |
| *Anas_platyrhynchos* | XM_005012054 |
| *Anolis carolinensis* | NM_001291387.1 |
| *Astyanax mexicanus* | U12328.1 |
| *Balaenoptera acutorostrata scammon* | XM_007192608.1 |
| *Bos mutus* | XM_005902834.1 |
| *Bos taurus* | NM_001014890.1 |
| *Bubalus bubalis* | XM_006078900.1 |
| *Callithrix jacchus* | XM_008982215.1 |
| *Callorhinchus milii* | NM_001292252.1 |
| *Camelus ferus* | XM_006180073.1 |
| *Canis familiaris* | X71380.1 |
| *Cavia porcellus* | NM_001173085.1 |
| *Ceratotherium simum simum* | XM_004442424.1 |
| *Chelonia mydas* | XM_007059947.1 |
| *Chinchilla lanigera* | XM_005387085.1 |
| *Chlorocebus sabaeus* | XM_007985378.1 |
| *Chrysemys picta bellii* | XM_008168043.1 |
| *Chrysochloris asiatica* | XM_006868670.1 |
| *Columba livia* | XM_005509036 |
| *Condylura cristata* | XM_004692360.1 |
| *Cricetulus griseus* | NM_001244407.1 |
| *Cynops pyrrhogaster* | AB043890.1 |
| *Danio rerio* | HM367063.1 |
| *Dasypus novemcinctus* | XM_004477246.1 |
| *Echinops telfairi* | XM_004702378.1 |
| *Elephantulus edwardii* | XM_006901040.1 |
| *Eptesicus fuscus* | XM_008152292.1 |
| *Equus caballus* | XM_001490301.3 |
| *Erinaceus europaeus* | XM_007517079.1 |
| *Falco peregrinus* | XM_005240222.1 |
| *Felis catus* | NM_001009242.1 |
| *Ficedula albicollis* | XM_005053322.1 |
| *Gallus gallus* | NM_001030606.1 |
| *Geospiza fortis* | XM_005426641.1 |
| *Gorilla gorilla gorilla* | XM_004036292.1 |
| *Haplochromis burtoni* | NM_001287832.1 |
| *Heterocephalus glaber* | XM_004902702.1 |
| *Homo sapiens* | NM_000539.3 |
| *Jaculus jaculus* | XM_004651581.1 |
| *Latimeria chalumnae* | XM_005997817.1 |
| *Lepisosteus oculatus* | XM_006630625.1 |
| *Lipotes vexillifer* | XM_007461564.1 |
| *Loxodonta africana* | NM_001280858.1 |
| *Macaca mulatta* | XM_001094250.1 |
| *Maylandia zebra* | AY775114.1 |
| *Meleagris gallopavo* | XM_003210211.2 |
| *Melopsittacus undulatus* | AF021242.1 |
| *Mesocricetus auratus* | XM_005066100.1 |
| *Microtus ochrogaster* | XM_005365058.1 |
| *Monodelphis domestica* | XM_001366188.2 |
| *Mus musculus* | BC031766.1 |
| *Mustela putorius furo* | XM_004738577.1 |

| | |
|---|---|
| *Myotis brandtii* | XM_005870029.1 |
| *Myotis davidii* | XM_006758300.1 |
| *Myotis lucifugus* | XM_006083811.1 |
| *Neolamprologus brichardi* | AY775110.1 |
| *Nomascus leucogenys* | XM_003265030.3 |
| *Ochotona princeps* | XM_004581320.1 |
| *Octodon degus* | XM_004645617.2 |
| *Odobenus rosmarus divergens* | XM_004395657.1 |
| *Orcinus orca* | XM_004284305.2 |
| *Oreochromis niloticus* | AY775108.1 |
| *Ornithorhynchus anatinus* | NM_001127627.1 |
| *Orycteropus afer afer* | XM_007956743 |
| *Oryctolagus cuniculus* | XM_008260202.1 |
| *Oryzias latipes* | AB180742.1 |
| *Ovis aries* | XM_004018534.2 |
| *Pan paniscus* | XM_003829435.2 |
| *Pan troglodytes* | XM_516740.5 |
| *Pantholops hodgsonii* | XM_005955745.1 |
| *Papio anubis* | XM_003906878.2 |
| *Pelodiscus sinensis* | XM_006132837.1 |
| *Peromyscus maniculatus bairdii* | XM_006978532.1 |
| *Petromyzon marinus* | AH005459.1 |
| *Physeter catodon* | XM_007126220.1 |
| *Poecilia formosa* | XM_007562291.1 |
| *Pongo abelii* | XM_002813145.3 |
| *Pseudopodoces humilis* | XM_005521947.1 |
| *Pteropus alecto* | XM_006917646.1 |
| *Pundamilia nyererei* | XM_005740519.1 |
| *Python bivittatus* | XM_007423262.1 |
| *Rattus norvegicus* | NM_033441.1 |
| *Saimiri boliviensis boliviensis* | XM_003926159.2 |
| *Sarcophilus harrisii* | XM_003762449.1 |
| *Sorex araneus* | XM_004613232.1 |
| *Spermophilus tridecemlineatus* | XM_005333784.1 |
| *Sus scrofa* | NM_214221.1 |
| *Taeniopygia guttata* | NM_001076695.1 |
| *Takifugu rubripes* | NM_001078631.1 |
| *Tarsius syrichta* | XM_008047820.1 |
| *Trichechus manatus* | AF055319.1 |
| *Tupaia chinensis* | XM_006160664.1 |
| *Tursiops truncatus* | NM_001280659.1 |
| *Vicugna pacos* | XM_006206787.1 |
| *Xenopus (Silurana) tropicalis* | NM_001097334.1 |
| *Xenopus laevis* | NM_001087048.1 |
| *Xiphophorus maculatus* | XM_005805648.1 |
| *Zonotrichia albicollis* | XM_005490154.1 |

**Vertebrate RPE65 data set:**

| | |
|---|---|
| *Ailuropoda melanoleuca* | XM_002924661 |
| *Alligator mississippiensis* | XM_006273833 |
| *Alligator sinensis* | XM_006037631 |
| *Ambystoma tigrinum* | AF047465 |
| *Anas platyrhynchos* | XM_005022335 |
| *Anolis carolinensis* | XM_003225837 |
| *Astyanax mexicanus* | XM_007254601 |
| *Astyanax mexicanus Mueller* | XM_007256147 |
| *Balaenoptera acutorostrata scammoni* | XM_007182907 |
| *Bos mutus* | XM_005906391 |
| *Bos taurus* | NM_174453 |
| *Bubalus bubalis* | XM_006052721 |
| *Callithrix jacchus* | XM_002750946 |

| | |
|---|---|
| *Callorhinchus milii* | XM_007909431 |
| *Camelus ferus* | XM_006191021 |
| *Canis lupus familiaris* | NM_001003176 |
| *Capra hircus* | XM_005678276 |
| *Cavia porcellus* | XM_003479100 |
| *Ceratotherium simum simum* | XM_004431484 |
| *Chelonia mydas* | XM_007063459 |
| *Chinchilla lanigera* | XM_005385268 |
| *Chlorocebus sabaeus* | XM_007978338 |
| *Chrysemys picta bellii* | XM_005300122 |
| *Chrysochloris asiatica* | XM_006862419 |
| *Columba livia* | XM_005498947 |
| *Condylura cristata* | XM_004679108 |
| *Cricetulus griseus* | XM_007622486 |
| *Cynops pyrrhogaster* | AB095018 |
| *Danio rerio (RPE65a)* | NM_200751 |
| *Danio rerio (RPE65b)* | NM_001089433 |
| *Danio rerio (RPE65c)* | NM_001113653 |
| *Dasypus novemcinctus* | XM_004483698 |
| *Echinops telfairi* | XM_004699612 |
| *Elephantulus edwardii* | XM_006879787 |
| *Eptesicus fuscus* | XM_008139423 |
| *Equus caballus* | XM_001498619 |
| *Erinaceus europaeus* | XM_007525692 |
| *Falco peregrinus* | XM_005244483 |
| *Felis catus* | XM_003990180 |
| *Ficedula albicollis* | XM_005050653 |
| *Gallus gallus* | NM_204884 |
| *Geospiza fortis* | XM_005429539 |
| *Gorilla gorilla* | XM_004025957 |
| *Haplochromis burtoni* | XM_005912639 |
| *Haplochromis burtoni Mueller* | XM_005951067 |
| *Heterocephalus glaber* | XM_004899378 |
| *Homo sapiens* | NM_000329 |
| *Jaculus jaculus* | XM_004671381 |
| *Latimeria chalumnae* | XM_006011611 |
| *Lepisosteus oculatus* | XM_006635249 |
| *Lipotes vexillifer* | XM_007460114 |
| *Loxodonta africana* | XM_003411238 |
| *Macaca mulatta* | XM_001095946 |
| *Maylandia zebra* | XM_004542781 |
| *Maylandia zebra Mueller* | XM_004562051 |
| *Meleagris gallopavo* | XM_003208913 |
| *Melopsittacus undulatus* | XM_005151194 |
| *Mesocricetus auratus* | XM_005086971 |
| *Microtus ochrogaster* | XM_005357442 |
| *Monodelphis domestica* | XM_007480405 |
| *Mus musculus* | NM_029987 |
| *Mustela putorius furo* | XM_004762993 |
| *Myotis brandtii* | XM_005861199 |
| *Myotis davidii* | XM_006770093 |
| *Myotis lucifugus* | XM_006099228 |
| *Neolamprologus brichardi* | XM_006786395 |
| *Neolamprologus brichardi Mueller* | XM_006797803 |
| *Nomascus leucogenys* | XM_003260179 |
| *Ochotona princeps* | XM_004588764 |
| *Octodon degus* | XM_004633990 |
| *Odobenus rosmarus divergens* | XM_004415169 |
| *Orcinus orca* | XM_004280749 |
| *Oreochromis niloticus* | XM_003437873 |
| *Oreochromis niloticus Mueller* | XM_005462114 |

| | |
|---|---|
| *Ornithorhynchus anatinus* | XM_007673238 |
| *Orycteropus afer afer* | XM_007959394 |
| *Oryctolagus cuniculus* | XM_002715929 |
| *Oryzias latipes* | XM_004079386 |
| *Oryzias latipes Mueller* | XM_004068058 |
| *Ovis aries* | XM_004002070 |
| *Pan paniscus* | XM_003807877 |
| *Pan troglodytes* | XM_009460457 |
| *Pantholops hodgsonii* | XM_005978384 |
| *Papio anubis* | XM_009210604 |
| *Pelodiscus sinensis* | XM_006123356 |
| *Peromyscus maniculatus bairdii* | XM_006996780 |
| *Petromyzon marinus* | JX115001 |
| *Physeter catodon* | XM_007116544 |
| *Poecilia formosa* | XM_007548703 |
| *Poecilia formosa Mueller* | XM_007543119 |
| *Pongo abelii* | XM_002810712 |
| *Pseudopodoces humilis* | XM_005521247 |
| *Pteropus alecto* | XM_006919310 |
| *Pundamilia nyererei* | XM_005721435 |
| *Pundamilia nyererei Mueller* | XM_005753540 |
| *Python bivittatus* | XM_007433578 |
| *Rattus norvegicus* | AF035673 |
| *Saimiri boliviensis* | XM_003921428 |
| *Sarcophilus harrisii* | XM_012547548 |
| *Sorex araneus* | XM_004607272 |
| *Spermophilus tridecemlineatus* | XM_005332357 |
| *Sus scrofa* | XM_003127931 |
| *Taeniopygia guttata* | XM_002187684 |
| *Takifugu rubripes* | XM_003975265 |
| *Takifugu rubripes Mueller* | XM_003977490 |
| *Tarsius syrichta* | XM_008048441 |
| *Trichechus manatus latirostris* | XM_004369044 |
| *Tupaia chinensis* | XM_006167148 |
| *Tursiops truncatus* | XM_004331382 |
| *Vicugna pacos* | XM_006205347 |
| *Xenopus laevis* | NM_001086800 |
| *Xenopus tropicalis* | NM_001127066 |
| *Xiphophorus maculatus* | XM_005807594 |
| *Xiphophorus maculatus Mueller* | XM_005805238 |
| *Zonotrichia albicollis* | XM_005496384 |

**Mammal RHO data set:**

| | |
|---|---|
| *Ailuropoda melanoleuca* | XM 002921249.2 |
| *Amblysomus hottentotus* | GQ290298 |
| *Artibeus jamaicensis* | GQ290299 |
| *Balaenoptera acutorostrata scammoni* | XM 007192608.1 |
| *Bathyergus suillus* | GQ290300 |
| *Bos mutus* | XM 005902834.1 |
| *Bos taurus* | NM 001014890.1 |
| *Bubalus bubalis* | XM 006078900.1 |
| *Caluromys philander* | AY313946.1 |
| *Camelus ferus* | XM 006180073.1 |
| *Canis lupus familiaris* | XM 005632035.1 |
| *Cavia porcellus* | NM 001173085.1 |
| *Ceratotherium simum simum* | XM 004442424.1 |
| *Chaerephon plicatus* | GQ290301.1 |
| *Chinchilla lanigera* | XM 005387085.1 |
| *Chlorocebus sabaeus* | XM 007985378.1 |
| *Chrysochloris asiatica* | XM 006868670.1 |
| *Condylura cristata* | XM 004692360.2 |

| | |
|---|---|
| *Cricetulus griseus* | NM 001244407.1 |
| *Cryptomys damarensis* | XM 010637946.1 |
| *Cynopterus brachyotis* | GQ290303 |
| *Cynopterus sphinx* | GQ863420.1 |
| *Dasypus novemcinctus* | XM 004477246.1 |
| *Delphinus delphis* | AF055314.1 |
| *Dobsonia viridis* | GQ290304 |
| *Echinops telfairi* | XM 004702378.1 |
| *Elephantulus edwardii* | XM 006901040.1 |
| *Enhydra lutris* | AY883931.1 |
| *Eonycteris spelaea* | GQ290305 |
| *Eptesicus fuscus* | XM 008152292.1 |
| *Equus caballus* | XM 001490301.3 |
| *Equus przewalskii* | XM 008531022.1 |
| *Erignathus barbatus* | AY883932.1 |
| *Erinaceus europaeus* | XM 007517079.1 |
| *Eubalaena glacialis* | JQ730751.1 |
| *Felis catus* | NM 001009242.1 |
| *Globicephala melas* | AF055315.1 |
| *Gorilla gorilla* | XM 004036292.1 |
| *Heterocephalus glaber* | XM 004902702.1 |
| *Hipposideros larvatus* | GQ290308.1 |
| *Hipposideros pomona* | GQ863426.1 |
| *Hipposideros pratti* | GQ290309.1 |
| *Homo sapiens* | AB464154.1 |
| *Hydrurga leptonyx* | AY883930.1 |
| *Jaculus jaculus* | XM 004651581.1 |
| *Leptonychotes weddellii* | XM 006740235.1 |
| *Lipotes vexillifer* | XM 007461564.1 |
| *Loxodonta africana* | NM 001280858.1 |
| *Macaca fascicularis* | NM 001283360.1 |
| *Macaca mulatta* | XM 001094250.1 |
| *Macroscelides proboscideus* | GQ290310 |
| *Megaderma spasma* | GQ290316.1 |
| *Mesocricetus auratus* | XM 005066100.1 |
| *Mesoplodon bidens* | AF055316.1 |
| *Microtus ochrogaster* | XM 005365058.1 |
| *Miniopterus fuliginosus* | GQ290311 |
| *Mirounga angustirostris* | AY228452.1 |
| *Monodelphis domestica* | XM 001366188.2 |
| *Mus musculus* | BC031766.1 |
| *Mustela putorius furo* | XM 004738577.1 |
| *Myotis brandtii* | XM 005870029.1 |
| *Myotis davidii* | XM 006758300.1 |
| *Myotis laniger* | GQ863435.1 |
| *Myotis lucifugus* | XM 006083811.1 |
| *Myotis ricketti* | GQ290312.1 |
| *Nomascus leucogenys* | XM 003265030.3 |
| *Nyctalus plancyi* | GQ863422.1 |
| *Nyctimene cephalotes* | GQ290313 |
| *Ochotona princeps* | XM 004581320.1 |
| *Octodon degus* | XM 004645617.2 |
| *Odobenus rosmarus divergens* | XM 004395657.1 |
| *Orcinus orca* | XM 004284305.2 |
| *Ornithorhynchus anatinus* | NM 001127627.1 |
| *Orycteropus afer afer* | XM 007956743.1 |
| *Oryctolagus cuniculus* | NM 001082349.1 |
| *Otolemur crassicaudatus* | AB112591.1 |
| *Ovis aries* | XM 004018534.2 |
| *Pan paniscus* | XM 003829435.2 |
| *Pan troglodytes* | XM_516740 |

| | |
|---|---|
| *Panthera tigris altaica* | XM 007075434.1 |
| *Pantholops hodgsonii* | XM 005955745.1 |
| *Papio anubis* | XM 003906878.2 |
| *Peromyscus maniculatus bairdii* | XM 006978532.1 |
| *Phoca groenlandica* | AF055318.1 |
| *Phoca vitulina* | AF055317.1 |
| *Physeter catodon* | XM 007126220.1 |
| *Pongo abelii* | XM 002813145.3 |
| *Pteropus alecto* | XM 006917646.1 |
| *Rattus norvegicus* | NM 033441.1 |
| *Rhinolophus ferrumequinum* | GQ290314.1 |
| *Rhinolophus pearsonii* | GQ863432.1 |
| *Rhinolophus pusillus* | GQ290315.1 |
| *Rhinolophus sinicus* | GQ863434.1 |
| *Rousettus leschenaultii* | GQ290317.1 |
| *Saimiri boliviensis boliviensis* | XM 003926159.2 |
| *Sarcophilus harrisii* | XM 003762449.1 |
| *Sminthopsis crassicaudata* | AY159786.2 |
| *Sorex araneus* | XM 004613232.1 |
| *Spalax ehrenbergi* | AF309568.1 |
| *Spermophilus tridecemlineatus* | XM 005333784.1 |
| *Sus scrofa* | NM 214221.1 |
| *Tachyglossus* | JX103830 |
| *Taphozous melanopogon* | GQ290318.1 |
| *Tarsius syrichta* | XM 008047820.1 |
| *Trichechus manatus* | AF055319.1 |
| *Tupaia chinensis* | XM 006160664.1 |
| *Tursiops truncatus* | NM 001280659.1 |
| *Ursus maritimus* | AY883926.1 |
| *Vicugna pacos* | XM_006206787.1 |
| *Zalophus californianus* | AY883924.1 |

**Mammal RPE65 data set:**

| | |
|---|---|
| *Ailuropoda melanoleuca* | XM_002924661 |
| *Balaenoptera acutorostrata scammoni* | XM_007182907 |
| *Bos mutus* | XM_005906391 |
| *Bos taurus* | NM_174453 |
| *Bubalus bubalis* | XM_006052721 |
| *Callithrix jacchus* | XM_002750946 |
| *Camelus ferus* | XM_010963423 |
| *Canis lupus familiaris* | NM_001003176 |
| *Capra hircus* | XM_005678276 |
| *Cavia porcellus* | XM_003479100 |
| *Ceratotherium simum simum* | XM_004431484 |
| *Chinchilla lanigera* | XM_005385268 |
| *Chlorocebus sabaeus* | XM_007978338 |
| *Chrysochloris asiatica* | XM_006862419 |
| *Condylura cristata* | XM_004679108 |
| *Cricetulus griseus* | XM_007622486 |
| *Dasypus novemcinctus* | XM_004483698 |
| *Echinops telfairi* | XM_004699612 |
| *Elephantulus edwardii* | XM_006879787 |
| *Eptesicus fuscus* | XM_008139423 |
| *Equus caballus* | XM_001498619 |
| *Erinaceus europaeus* | XM_007525692 |
| *Felis catus* | XM_003990180 |
| *Gorilla gorilla* | XM_004025957 |
| *Heterocephalus glaber* | XM_004899378 |
| *Homo sapiens* | KJ892021 |
| *Jaculus jaculus* | XM_004671381 |
| *Lipotes vexillifer* | XM_007460114 |

| | |
|---|---|
| *Loxodonta africana* | XM_003411238 |
| *Macaca mulatta* | XM_001095946 |
| *Mesocricetus auratus* | XM_005086971 |
| *Microtus ochrogaster* | XM_005357442 |
| *Monodelphis domestica* | XM_007480405 |
| *Mus musculus* | NM_029987 |
| *Mustela putorius furo* | XM_004762993 |
| *Myotis brandtii* | XM_005861199 |
| *Myotis davidii* | XM_006770093 |
| *Myotis lucifugus* | XM_006099228 |
| *Nomascus leucogenys* | XM_003260179 |
| *Ochotona princeps* | XM_004588764 |
| *Octodon degus* | XM_004633990 |
| *Odobenus rosmarus divergens* | XM_004415169 |
| *Orcinus orca* | XM_004280749 |
| *Ornithorhynchus anatinus* | XM_007673238 |
| *Orycteropus afer* | XM_007959394 |
| *Oryctolagus cuniculus* | XM_002715929 |
| *Ovis aries* | XM_004002070 |
| *Pan paniscus* | XM_003807877 |
| *Pan troglodytes* | XM_009460457 |
| *Pantholops hodgsonii* | XM_005978384 |
| *Papio anubis* | XM_009210604 |
| *Peromyscus maniculatus bairdii* | XM_006996780 |
| *Physeter catodon* | XM_007116544 |
| *Pongo abelii* | XM_002810712 |
| *Pteropus alecto* | XM_006919310 |
| *Rattus norvegicus* | AF035673 |
| *Saimiri boliviensis* | XM_003921428 |
| *Sarcophilus harrisii* | XM_012547548 |
| *Sorex araneus* | XM_004607272 |
| *Spermophilus tridecemlineatus* | XM_005332357 |
| *Sus scrofa* | XM_003127931 |
| *Tarsius syrichta* | XM_008048441 |
| *Trichechus manatus latirostris* | XM_004369044 |
| *Tupaia chinensis* | XM_006167148 |
| *Tursiops truncatus* | XM_004331382 |
| *Vicugna pacos* | XM_006205347 |

**Supplemental table 2.** Rhodopsin disease sites found in various mutation databases (OMIM, dbSNP, UniProt, HGMD) used in analyses. Vertebrate, mammal, and human amino acid numberings are listed. RHO disease sites confirmed to be pathogenic via *in vitro* or family co-segregating studies are also listed with references.

| All Pathogenic Sites | | | 53 Confirmed Pathogenic Sites | | | |
|---|---|---|---|---|---|---|
| **Vert** | **Mamm** | **Human** | **Vert** | **Mamm** | **Human** | **References** |
| 4 | 4 | 4 | 4 | 4 | 4 | Kaushal & Khorana, 1994 |
| 15 | 15 | 15 | 15 | 15 | 15 | Kaushal et al., 1994 |
| 17 | 17 | 17 | 17 | 17 | 17 | Sung et al., 1991; Kaushal & Khorana, 1994; Kaushal et al., 1994 |
| 20 | 20 | 20 | 23 | 23 | 23 | Sung et al., 1991; 1993; Olsson et al., 1992; Kaushal & Khorana, 1994; McKibbin et al., 2007 |
| 23 | 23 | 23 | 28 | 28 | 28 | Kaushal & Khorana, 1994 |
| 28 | 28 | 28 | 44 | 44 | 44 | Andrés et al., 2003; Bosch et al., 2003; Piechnick et al., 2012 |
| 40 | 40 | 40 | 45 | 45 | 45 | Matias-Florentino et al., 2009, but see Vincent et al., 2013 |
| 44 | 44 | 44 | 51 | 51 | 51 | Kaushal & Khorana, 1994; Hwa et al., 1997; Bosch et al., 2003; Bosch-Presegué et al., 2011 |
| 45 | 45 | 45 | 53 | 53 | 53 | Sung et al., 1993 |
| 46 | 46 | 46 | 58 | 58 | 58 | Min et al., 1993 |
| 51 | 51 | 51 | 64 | 64 | 64 | Shi et al., 1995 |
| 52 | 52 | 52 | 87 | 87 | 87 | Sung et al., 1991; Kaushal & Khorana, 1994; Bosch et al., 2003 |
| 53 | 53 | 53 | 88 | 88 | 88 | Audo et al., 2010 |
| 56 | 56 | 56 | 89 | 89 | 89 | Hwa et al., 1997;Sung et al., 1991; Bosch et al., 2003 |
| 57 | 57 | 57 | 90 | 90 | 90 | Rao et al., 1994; Gross et al., 2003*b*; Bosch-Presegué et al., 2011; Toledo et al., 2011; Singhal et al., 2013 |
| 58 | 58 | 58 | 94 | 94 | 94 | Gross et al., 2003*a*; 2003*b*; Janz & Farrens, 2004; Piechnick et al., 2012 |
| 64 | 64 | 64 | 106 | 106 | 106 | Sung et al., 1991; Kaushal & Khorana, 1994 |
| 78 | 78 | 78 | 110 | 110 | 110 | Karnik et al., 1988; Hwa et al., 1999; Krebs et al., 2010 |
| 87 | 87 | 87 | 114 | 114 | 114 | Dryja et al., 2000*a* |
| 88 | 88 | 88 | 125 | 125 | 125 | Sung et al., 1993; Garriga et al., 1996 |
| 89 | 89 | 89 | 127 | 127 | 127 | Garriga et al., 1996 |
| 90 | 90 | 90 | 135 | 135 | 135 | Sakmar et al., 1989; Weitz & Nathans, 1993; Min et al., 1993; Sung et al., 1993; Acharya & Karnik, 1996 |
| 94 | 94 | 94 | 137 | 137 | 137 | Andrés et al., 2003 |
| 104 | 104 | 104 | 140 | 140 | 140 | Natochin et al., 2003; Yamashita et al., 2000 |
| 106 | 106 | 106 | 150 | 150 | 150 | Zhu et al., 2006; Zhang et al., 2012 |
| 109 | 109 | 109 | 161 | 161 | 161 | Kartasasmita et al., 2011 |
| 110 | 110 | 110 | 164 | 164 | 164 | Hwa et al., 1997 |
| 114 | 114 | 114 | 167 | 167 | 167 | Dryja et al., 1991; Sung et al., 1993; Kaushal & Khorana, 1994; Breikers et al., 2002 |
| 122 | 122 | 122 | 171 | 171 | 171 | Antiñolo et al., 1994; Dryja et al., 1991; Sung et al., 1993; Kaushal & Khorana, 1994; Vaithinathan et al., 1994 |
| 125 | 125 | 125 | 178 | 178 | 178 | Sung et al., 1991; Kaushal & Khorana, 1994 |
| 127 | 127 | 127 | 180 | 180 | 180 | Iannaccone et al., 2006 |
| 131 | 131 | 131 | 181 | 181 | 181 | Dryja et al., 1991; Sung et al., 1993; Kaushal & Khorana, 1994; Yan et al., 2002; Lewis et al., 2004; Janz & Farrens, 2004; Lüdeke et al., 2005; Feldman et al., 2012 |
| 135 | 135 | 135 | 182 | 182 | 182 | Fishman et al., 1992; Sung et al., 1993 |
| 136 | 136 | 136 | 184 | 184 | 184 | Dryja et al., 2000 |
| 137 | 137 | 137 | 185 | 185 | 185 | Karnik et al., 1988; McKibbin et al., 2007 |
| 140 | 140 | 140 | 186 | 186 | 186 | Liu et al., 2013; Sung et al., 1993; Kaushal & Khorana, 1994; Janz & Farrens, 2004; Yan et al., 2007; Liu et al., 2011; Piechnick et al., 2012 |
| 150 | 150 | 150 | 187 | 187 | 187 | Hwa et al., 1999;Karnik et al., 1988 |
| 160 | 160 | 160 | 188 | 188 | 188 | Dryja et al., 1991; Sung et al., 1993; Kaushal & Khorana, 1994 |
| 161 | 161 | 161 | 190 | 190 | 190 | Sung et al., 1991; Kaushal & Khorana, 1994; Janz et al., 2003; Liu et al., 2013 |
| 164 | 164 | 164 | 207 | 207 | 207 | Aguilà et al., 2009; Piechnick et al., 2012 |
| 167 | 167 | 167 | 211 | 211 | 211 | Weitz & Nathans, 1992; Sung et al., 1993; Kaushal & Khorana, 1994; Hwa et al., 1997; Lewis et al., 2006 |
| 170 | 170 | 170 | 222 | 222 | 222 | Kaushal & Khorana, 1994 |
| 171 | 171 | 171 | 249 | 249 | 249 | Rosenfeld et al., 1995 |

**All Pathogenic Sites**

| Vert | Mamm | Human |
|---|---|---|
| 176 | 176 | 176 |
| 178 | 178 | 178 |
| 179 | 179 | 179 |
| 180 | 180 | 180 |
| 181 | 181 | 181 |
| 182 | 182 | 182 |
| 184 | 184 | 184 |
| 185 | 185 | 185 |
| 186 | 186 | 186 |
| 187 | 187 | 187 |
| 188 | 188 | 188 |
| 190 | 190 | 190 |
| 193 | 193 | 193 |
| 207 | 207 | 207 |
| 209 | 209 | 209 |
| 211 | 211 | 211 |
| 215 | 215 | 215 |
| 216 | 216 | 216 |
| 220 | 220 | 220 |
| 222 | 222 | 222 |
| 249 | 249 | 249 |
| 252 | 252 | 252 |
| 267 | 267 | 267 |
| 270 | 270 | 270 |
| 284 | 284 | 284 |
| 289 | 289 | 289 |
| 292 | 292 | 292 |
| 295 | 295 | 295 |
| 296 | 296 | 296 |
| 297 | 297 | 297 |
| 311 | 311 | 311 |
| 312 | 312 | 312 |
| 328 | 328 | 328 |
| 343 | 341 | 341 |
| 349 | 347 | 342 |
| 350 | 348 | 343 |
| 351 | 349 | 344 |
| 352 | 350 | 345 |
| 353 | 351 | 346 |
| 354 | 352 | 347 |

**53 Confirmed Pathogenic Sites**

| Vert | Mam | Human | Reference |
|---|---|---|---|
| 292 | 292 | 292 | Weitz & Nathans, 1992; Dryja et al., 1993; Jin et al., 2003 |
| 296 | 296 | 296 | Robinson et al., 1992; Kaushal & Khorana, 1994 |
| 297 | 297 | 297 | Hwa et al., 1997 |
| 343 | 341 | 341 | Zhao et al., 2001 |
| 349 | 347 | 342 | Scott et al., 1993 |
| 350 | 348 | 343 | Zhang et al., 1997 |
| 351 | 349 | 344 | Concepcion & Chen, 2010 |
| 352 | 350 | 345 | Dryja et al., 1991 |
| 354 | 352 | 347 | Berson et al., 1991; Sung et al., 1991; Li et al., 1996; Banin et al., 1999 |

**Supplemental table 3.** RPE65 pathogenic sites found in various mutation databases (OMIM, dbSNP, UniProt, HGMD) used in analyses. Vertebrate, mammal, and human amino acid numberings are consistent.

| All disease sites | |
|---|---|
| **Human** | **Human** |
| 1 | 417 |
| 6 | 431 |
| 22 | 434 |
| 25 | 435 |
| 32 | 436 |
| 40 | 443 |
| 44 | 452 |
| 60 | 457 |
| 64 | 460 |
| 68 | 462 |
| 70 | 470 |
| 79 | 473 |
| 85 | 515 |
| 91 | 528 |
| 95 | 533 |
| 101 | |
| 102 | |
| 104 | |
| 118 | |
| 124 | |
| 132 | |
| 144 | |
| 148 | |
| 162 | |
| 167 | |
| 182 | |
| 205 | |
| 215 | |
| 234 | |
| 239 | |
| 244 | |
| 249 | |
| 251 | |
| 287 | |
| 294 | |
| 303 | |
| 313 | |
| 318 | |
| 321 | |
| 330 | |
| 341 | |
| 343 | |
| 360 | |
| 363 | |
| 368 | |
| 370 | |
| 393 | |
| 402 | |
| 403 | |
| 407 | |
| 408 | |

**Supplemental table 4.** Random sites (PAML) analyses for RHO based on the Bayesian vertebrate and mammal trees

| Tree | Model | np | lnL | k | Parameters | | | | Null | LRT | df | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vertebrate | M0 | 199 | -25222.6 | 2.52 | | 0.05538 | | | n/a | | | |
| | M1a | 200 | -24968.5 | 2.67 | **p:** | 0.935 | 0.065 | | M0 | 508.0 | 1 | **0.0000** |
| | | | | | **w:** | 0.045 | 1.000 | | | | | |
| | M2a | 202 | -24968.5 | 2.67 | **p:** | 0.935 | 0.065 | 0.000 | M1a | 0.0 | 2 | **1.0000** |
| | | | | | **w:** | 0.045 | 1.000 | 5.230 | | | | |
| | M3 | 203 | -24324.9 | 2.53 | **p:** | 0.628 | 0.268 | 0.105 | M0 | 1795.4 | 4 | **0.0000** |
| | | | | | **w:** | 0.007 | 0.095 | 0.313 | | | | |
| | M7 | 200 | -24306.5 | 2.53 | **p:** | 0.267 | **q:** | 3.279 | n/a | | | |
| | M8a | 201 | -24301.0 | 2.53 | **p:** | 0.281 | **q:** | 3.955 | n/a | | | |
| | | | | | **p1:** | 0.006 | **w:** | 1.000 | | | | |
| | M8 | 202 | -24301.0 | 2.53 | **p:** | 0.281 | **q:** | 3.955 | M7 | 11.0 | 2 | **0.0042** |
| | | | | | **p1:** | 0.006 | **w:** | 1.000 | M8a | 0.0 | 1 | **1.0000** |
| Mammal | M0 | 213 | -18022.4 | 4.19 | | 0.04136 | | | n/a | | | |
| | M1a | 214 | -17762.4 | 4.38 | **p:** | 0.959 | 0.041 | | M0 | 520.0 | 1 | **0.0000** |
| | | | | | **w:** | 0.032 | 1.000 | | | | | |
| | M2a | 216 | -17762.4 | 4.38 | **p:** | 0.959 | 0.000 | 0.041 | M1a | 0.0 | 2 | **1.0000** |
| | | | | | **w:** | 0.032 | 1.000 | 1.000 | | | | |
| | M3 | 217 | -17324.0 | 4.29 | **p:** | 0.767 | 0.194 | 0.039 | M0 | 1396.9 | 4 | **0.0000** |
| | | | | | **w:** | 0.006 | 0.130 | 0.463 | | | | |
| | M7 | 214 | -17319.8 | 4.28 | **p:** | 0.163 | **q:** | 2.032 | n/a | | | |
| | M8 | 216 | -17319.8 | 4.28 | **p:** | 0.163 | **q:** | 2.032 | M7 | 0.0 | 2 | **1.0000** |
| | | | | | **p1:** | 0.000 | **w:** | 1.000 | | | | |

Note: np, number of parameters; ln L, ln likelihood; κ, transition/transversion ratio; df, degrees of freedom. For models M7-M8, p and q describe the shape of the beta distribution, and $\omega_p$ refers to the positively selected site class (with proportion in parentheses) for models M8 and M8a (where it is constrained to one).

**Supplemental table 5.** Random sites (PAML) analyses for RPE65 based on the Bayesian vertebrate and mammal trees

| Tree | Model | np | lnL | k | Parameters | | | | Null | LRT | df | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vertebrate | M0 | 222 | -41156.4 | 2.09 | | 0.06459 | | | n/a | | | |
| | M1a | 223 | -40986.4 | 2.09 | **p:** | 0.972 | 0.028 | | M0 | 339.9 | 1 | **0.0000** |
| | | | | | **w:** | 0.060 | 1.000 | | | | | |
| | M2a | 225 | -40986.4 | 2.19 | **p:** | 0.972 | 0.028 | 0.000 | M1a | 0.0 | 2 | **1.0000** |
| | | | | | **w:** | 0.060 | 1.000 | 999.000 | | | | |
| | M3 | 226 | -40188.4 | 2.09 | **p:** | 0.513 | 0.345 | 0.142 | M0 | 1935.9 | 4 | **0.0000** |
| | | | | | **w:** | 0.007 | 0.086 | 0.254 | | | | |
| | M7 | 223 | -40170.4 | 2.09 | **p:** | 0.397 | **q:** | 4.698 | n/a | | | |
| | M8a | 224 | -40159.8 | 2.09 | **p:** | 0.408 | **q:** | 5.155 | n/a | | | |
| | | | | | **p1:** | 0.002 | **w:** | 1.000 | | | | |
| | M8 | 225 | -40159.0 | 2.09 | **p:** | 0.408 | **q:** | 5.143 | M7 | 22.7 | 2 | **0.0000** |
| | | | | | **p1:** | 0.002 | **w:** | 1.350 | M8a | 1.5 | 1 | **0.2146** |
| Mammal | M0 | 125 | -16164.7 | 2.99 | | 0.05513 | | | n/a | | | |
| | M1a | 126 | -16063.6 | 3.18 | **p:** | 0.955 | 0.045 | | M0 | 202.2 | 1 | **0.0000** |
| | | | | | **w:** | 0.040 | 1.000 | | | | | |
| | M2a | 128 | -16063.6 | 3.17 | **p:** | 0.955 | 0.045 | 0.000 | M1a | 0.0 | 2 | **1.0000** |
| | | | | | **w:** | 0.040 | 1.000 | 6.196 | | | | |
| | M3 | 129 | -15913.5 | 2.99 | **p:** | 0.735 | 0.206 | 0.059 | M0 | 502.4 | 4 | **0.0000** |
| | | | | | **w:** | 0.008 | 0.136 | 0.406 | | | | |
| | M7 | 126 | -15914.4 | 2.99 | **p:** | 0.210 | **q:** | 3.051 | n/a | | | |
| | M8 | 128 | -15914.2 | 2.99 | **p:** | 0.213 | **q:** | 3.184 | M7 | 0.5 | 2 | **0.7922** |
| | | | | | **p1:** | 0.001 | **w:** | 1.000 | | | | |

Note: np, number of parameters; ln L, ln likelihood; κ, transition/transversion ratio; df, degrees of freedom. For models M7-M8, p and q describe the shape of the beta distribution, and $\omega_p$ refers to the positively selected site class (with proportion in parentheses) for models M8 and M8a (where it is constrained to one).

**Supplemental table 6.** Vertebrate RHO and RPE65 all pathogenic vs. non-pathogenic $d_N/d_S$ site estimates produced by FUBAR, FEL and M8 compared with Mann-Whitney tests

| Tree | Gene | Molecular evolutionary analysis | Pathogenic site N | Non-pathogenic site N | Pathogenic Mean Rank[2] | Non-pathogenic Mean Rank[2] | U | Z | p |
|---|---|---|---|---|---|---|---|---|---|
| ML | RHO | FUBAR | 84 | 271 | 34.99 | 143 | 8853 | -3.077 | **0.0021** |
| | RHO | FEL[1] | 81 | 261 | 33.98 | 137.5 | 8301 | -3.037 | **0.0024** |
| | RHO | M8 | 84 | 271 | 37.02 | 141 | 9657 | -2.417 | **0.0156** |
| ML | RPE65 | FUBAR | 66 | 467 | 26.17 | 240.8 | 11740 | -3.136 | **0.0017** |
| | RPE65 | FEL[1] | 66 | 465 | 25.37 | 240.6 | 11260 | -3.582 | **0.0003** |
| | RPE65 | M8 | 66 | 467 | 26.72 | 240.3 | 12030 | -3.222 | **0.0013** |
| Bayes | RHO | FUBAR | 84 | 271 | 34.89 | 143.1 | 8817 | -3.121 | **0.0018** |
| | RHO | FEL[1] | 81 | 260 | 33.88 | 137.1 | 8234 | -3.082 | **0.0021** |
| | RHO | M8 | 84 | 271 | 37.37 | 140.6 | 9695 | -2.490 | **0.0128** |
| Bayes | RPE65 | FUBAR | 66 | 467 | 26.33 | 240.7 | 11830 | -3.061 | **0.0022** |
| | RPE65 | FEL[1] | 66 | 465 | 25.58 | 240.4 | 11370 | -3.487 | **0.0005** |
| | RPE65 | M8 | 66 | 467 | 26.84 | 240.2 | 12090 | -3.168 | **0.0015** |

1. FEL $d_N/d_S$ site estimates for all datasets were corrected to remove undefined and infinite values before Mann-Whitney tests.
2. Mann-Whitney *U* statistics were calculated for pathogenic vs non-pathogenic $d_N/d_S$ mean ranks for all RHO and RPE65 datasets.

**Supplemental table 7.** Results of Mann-Whitney tests between FUBAR-estimated $d_N/d_S$ of pathogenic vs non pathogenic sites.

| Tree | Gene | Pathogenic sites | Dataset | Pathogenic site N | Non-pathogenic site N | Pathogenic Mean Rank | Non-Pathogenic Mean Rank | U | Z | p |
|---|---|---|---|---|---|---|---|---|---|---|
| ML | RHO | Confirmed | Vertebrate | 53 | 302 | 17.54 | 160.5 | 4795 | -4.655 | **0.0000** |
| | RHO | Confirmed | Mammal | 53 | 302 | 20.08 | 156.9 | 5657 | -3.347 | **0.0008** |
| | RHO | All | Vertebrate | 84 | 271 | 34.99 | 143 | 8853 | -3.077 | **0.0021** |
| | RHO | All | Mammal | 84 | 269 | 36.67 | 140.3 | 9374 | -2.356 | **0.0185** |
| | RPE65 | All | Vertebrate | 66 | 467 | 26.17 | 240.8 | 11740 | -3.136 | **0.0017** |
| | RPE65 | All | Mammal | 66 | 467 | 29.61 | 237.4 | 13570 | -1.569 | 0.1166 |
| Bayes | RHO | Confirmed | Vertebrate | 53 | 302 | 17.47 | 160.5 | 4770 | -4.691 | **0.0000** |
| | RHO | Confirmed | Mammal | 53 | 302 | 20.11 | 156.9 | 5667 | -3.333 | **0.0009** |
| | RHO | All | Vertebrate | 84 | 271 | 34.89 | 143.1 | 8817 | -3.121 | **0.0018** |
| | RHO | All | Mammal | 84 | 269 | 36.7 | 140.3 | 9384 | -2.344 | **0.0191** |
| | RPE65 | Full | Vertebrate | 66 | 467 | 26.33 | 240.7 | 11830 | -3.061 | **0.0022** |
| | RPE65 | Full | Mammal | 66 | 467 | 29.6 | 237.4 | 13560 | -1.577 | 0.1148 |

**Supplemental table 8.** Results of Mann-Whitney tests between FEL estimated $d_N$-$d_S$ of pathogenic vs non pathogenic sites.

| Tree | Gene | Pathogenic Sites | Dataset | Pathogenic site N | Non-pathogenic site N | Pathogenic Mean Rank | Non-Pathogenic Mean Rank | U | Z | p |
|---|---|---|---|---|---|---|---|---|---|---|
| ML | RHO | Confirmed | Vert | 53 | 302 | 21.89 | 156.1 | 6339 | -2.414 | **0.0158** |
| | RHO | Confirmed | Mamm | 53 | 302 | 22.05 | 155 | 6352 | -2.333 | **0.0197** |
| | RHO | All | Vert | 84 | 271 | 39.38 | 138.6 | 10410 | -1.181 | 0.2376 |
| | RHO | All | Mamm | 84 | 269 | 38.69 | 138.3 | 10090 | -1.480 | 0.1388 |
| | RPE65 | All | Vert | 66 | 467 | 27.12 | 239.9 | 12240 | -2.705 | **0.0068** |
| | RPE65 | All | Mamm | 66 | 467 | 30.71 | 236.3 | 14160 | -1.068 | 0.2854 |
| Bayes | RHO | Confirmed | Vert | 53 | 302 | 21.69 | 156.3 | 6271 | -2.514 | **0.0120** |
| | RHO | Confirmed | Mamm | 53 | 302 | 22.09 | 154.9 | 6367 | -2.311 | **0.0208** |
| | RHO | All | Vert | 84 | 271 | 39.15 | 138.9 | 10330 | -1.283 | 0.1996 |
| | RHO | All | Mamm | 84 | 269 | 38.68 | 138.3 | 10080 | -1.488 | 0.1367 |
| | RPE65 | All | Vert | 66 | 467 | 26.98 | 240 | 12170 | -2.767 | **0.0057** |
| | RPE65 | All | Mamm | 66 | 467 | 30.72 | 236.3 | 14160 | -1.066 | 0.2862 |

**Supplemental table 9.** Vertebrate RHO disease vs. non-disease *dN* and *dS* site estimates calculated from FUBAR.

| Tree | Gene | Pathogenic Sites | Metric | Pathogenic site N | Non-pathogenic site N | Pathogenic Mean Rank | Non-pathogenic Mean Rank | U | Z | p |
|---|---|---|---|---|---|---|---|---|---|---|
| ML | RHO | Confirmed | *dN* | 53 | 302 | 18.41 | 159.6 | 5103 | -4.208 | **0.0000** |
| | RHO | Confirmed | *dS* | 53 | 302 | 30.81 | 147.2 | 6500 | -2.180 | **0.0293** |
| | RHO | All | *dN* | 84 | 271 | 34.86 | 143.1 | 8806 | -3.134 | **0.0017** |
| | RHO | All | *dS* | 84 | 271 | 43.19 | 134.8 | 11000 | -0.464 | 0.6425 |
| | RPE65 | All | *dN* | 66 | 467 | 27.61 | 239.4 | 12510 | -2.479 | **0.0132** |
| | RPE65 | All | *dS* | 66 | 467 | 38.17 | 228.8 | 12690 | -2.324 | **0.0201** |
| Bayes | RHO | Confirmed | *dN* | 53 | 302 | 18.41 | 159.6 | 5102 | -4.209 | **0.0000** |
| | RHO | Confirmed | *dS* | 53 | 302 | 30.81 | 147 | 6441 | -2.266 | **0.0235** |
| | RHO | All | *dN* | 84 | 271 | 34.86 | 143.1 | 8806 | -3.134 | **0.0017** |
| | RHO | All | *dS* | 84 | 271 | 43.19 | 134.5 | 10900 | -0.588 | 0.5563 |
| | RPE65 | All | *dN* | 66 | 467 | 27.61 | 239.2 | 12620 | -2.384 | **0.0171** |
| | RPE65 | All | *dS* | 66 | 467 | 38.17 | 228.7 | 12610 | -2.391 | **0.0168** |

ACHARYA S & KARNIK SS (1996). Modulation of GDP release from transducin by the conserved Glu134-Arg135 sequence in rhodopsin. *Journal of Biological Chemistry* **271,** 25406–25411.

AGUILÀ M, TOLEDO D, MORILLO M, DOMINGUEZ M, VAZ B, ALVAREZ R, DE LERA AR & GARRIGA P (2009). Structural coupling of 11-cis-7-methyl-retinal and amino acids at the ligand binding pocket of rhodopsin. *Photochemistry and Photobiology* **85,** 485–493.

ANDRÉS A, GARRIGA P & MANYOSA J (2003). Altered functionality in rhodopsin point mutants associated with retinitis pigmentosa. *Biochemical and Biophysical Research Communications* **303,** 294–301.

ANTIÑOLO G, SÁNCHEZ B, BORREGO S, RUEDA T, CHAPARRO P & CABEZA JC (1994). Identification of a new mutation at codon 171 of rhodopsin gene causing autosomal dominant retinitis pigmentosa. *Human Molecular Genetics* **3,** 1421.

AUDO I, FRIEDRICH A, MOHAND-SAÏD S, LANCELOT M-E, ANTONIO A, MOSKOVA-DOUMANOVA V, POCH O, BHATTACHARYA S, SAHEL J-A & ZEITZ C (2010). An unusual retinal phenotype associated with a novel mutation in RHO. *Archives of Ophthalmology* **128,** 1036–1045.

BANIN E, CIDECIYAN AV, ALEMAN TS, PETTERS RM, WONG F, MILAM AH & JACOBSON SG (1999). Retinal rod photoreceptor-specific gene mutation perturbs cone pathway development. *Neuron* **23,** 549–557.

BERSON EL, ROSNER B, SANDBERG MA, WEIGEL-DIFRANCO C & DRYJA TP (1991). Ocular findings in patients with autosomal dominant retinitis pigmentosa and rhodopsin, proline-347-leucine. *American Journal of Ophthalmology* **111,** 614–623.

BOSCH L, RAMON E, DEL VALLE LJ & GARRIGA P (2003). Structural and functional role of helices I and II in rhodopsin: A novel interplay evidenced by mutations at gly-51 and gly-89 in the transmembrane domain. *Journal of Biological Chemistry* **278,** 20203–20209.

BOSCH-PRESEGUÉ L, RAMON E, TOLEDO D, CORDOMÍ A & GARRIGA P (2011). Alterations in the photoactivation pathway of rhodopsin mutants associated with retinitis pigmentosa. *FEBS Journal* **278,** 1493–1505.

BREIKERS G, PORTIER-VANDELUYTGAARDEN MJM, BOVEE-GEURTS PHM & DEGRIP WJ (2002). Retinitis pigmentosa-associated rhodopsin mutations in three membrane-located cysteine residues present three different biochemical phenotypes. *Biochemical and Biophysical Research Communications* **297,** 847–853.

CONCEPCION F & CHEN J (2010). Q344ter Mutation Causes Mislocalization of Rhodopsin Molecules That Are Catalytically Active: A Mouse Model of Q344ter-Induced Retinal Degeneration ed. Lewin A. *PLoS ONE* **5,** e10904–e10914.

DRYJA TP, BERSON EL, RAO VR & OPRIAN DD (1993). Heterozygous missense mutation in the rhodopsin gene as a cause of congenital stationary night blindness. *Nature Genetics* **4,** 280–283.

DRYJA TP, HAHN LB, COWLEY GS, MCGEE TL & BERSON EL (1991). Mutation spectrum of the rhodopsin gene among patients with autosomal dominant retinitis pigmentosa. *Proceedings of the National Academy of Sciences U.S.A.* **88,** 9370–9374.

DRYJA TP, MCEVOY JA, MCGEE TL & BERSON EL (2000). Novel rhodopsin mutations Gly114Val and Gln184Pro in dominant retinitis pigmentosa. *Investigative Ophthalmology & Visual Science* **41,** 3124–3127.

FELDMAN T, OSTROVSKY M & KHOLMURODOV K (2012). Model of Abnormal chromophore-protein interaction for E181K rhodopsin mutation: computer Molecular dynamics s tudy. *The Open Biochemistry Journal* **6,** 94–102.

FISHMAN GA, STONE EM, SHEFFIELD VC, GILBERT LD & KIMURA AE (1992). Ocular findings associated with rhodopsin gene codon 17 and codon 182 transition mutations in dominant retinitis pigmentosa. *Archives of Ophthalmology* **110,** 54–62.

GARRIGA P, LIU X & KHORANA HG (1996). Structure and function in rhodopsin: correct folding and misfolding in point mutants at and in proximity to the site of the retinitis pigmentosa mutation Leu-125-->Arg in the transmembrane helix C. *Proceedings of the National Academy of Sciences U.S.A.* **93,** 4560–4564.

GROSS AK, RAO VR & OPRIAN DD (2003*a*). Characterization of rhodopsin congenital night blindness mutant T94I. *Biochemistry* **42,** 2009–2015.

GROSS AK, XIE G & OPRIAN DD (2003*b*). Slow binding of retinal to rhodopsin mutants G90D and T94D. *Biochemistry* **42,** 2002–2008.

HWA J, GARRIGA P, LIU X & KHORANA HG (1997). Structure and function in rhodopsin: packing of the helices in the transmembrane domain and folding to a tertiary structure in the intradiscal domain are coupled. *Proceedings of the National Academy of Sciences U.S.A.* **94,** 10571–10576.

HWA J, REEVES PJ, KLEIN-SEETHARAMAN J, DAVIDSON F & KHORANA HG (1999). Structure and function in rhodopsin: further elucidation of the role of the intradiscal cysteines, Cys-110, -185, and -187, in rhodopsin folding and function. *Proceedings of the National Academy of Sciences U.S.A.* **96,** 1932–1935.

IANNACCONE A, MAN D, WASEEM N, JENNINGS BJ, GANAPATHIRAJU M, GALLAHER K, REESE E, BHATTACHARYA SS & KLEIN-SEETHARAMAN J (2006). Retinitis pigmentosa associated with rhodopsin mutations: Correlation between phenotypic variability and molecular effects. *Vision Research* **46,** 4556–4567.

JANZ JM & FARRENS DL (2004). Role of the retinal hydrogen bond network in rhodopsin schiff base stability and hydrolysis. *Journal of Biological Chemistry* **279,** 55886–55894.

JANZ JM, FAY JF & FARRENS DL (2003). Stability of dark state rhodopsin is mediated by a conserved ion pair in intradiscal loop E-2. *Journal of Biological Chemistry* **278,** 16982–16991.

JIN S, CORNWALL MC & OPRIAN DD (2003). Opsin activation as a cause of congenital night blindness. *Nature Neuroscience* **6,** 731–735.

KARNIK SS, SAKMAR TP, CHEN HB & KHORANA HG (1988). Cysteine residues 110 and 187 are essential for the formation of correct structure in bovine rhodopsin. *Proceedings of the National Academy of Sciences U.S.A* **85,** 8459–8463.

KARTASASMITA A, FUJIKI K, ISKANDAR E, SOVANI I, FUJIMAKI T & MURAKAMI A (2011). A novel nonsense mutation in Rhodopsin gene in two Indonesian Families with Autosomal Recessive Retinitis Pigmentosa. *Ophthalmic Genetics* **32,** 57–63.

KAUSHAL S & KHORANA HG (1994). Structure and function in rhodopsin. 7. Point mutations associated with autosomal dominant retinitis pigmentosa. *Biochemistry*; **33,** 6121-6128.

KAUSHAL S, RIDGE KD & KHORANA HG (1994). Structure and function in rhodopsin: the role of asparagine-linked glycosylation. *Proceedings of the National Academy of Sciences U.S.A.* **91,** 4024–4028.

KREBS MP, HOLDEN DC, JOSHI P, CLARK CL III, LEE AH & KAUSHAL S (2010). Molecular mechanisms of rhodopsin retinitis pigmentosa and the efficacy of pharmacological rescue. *Journal of Molecular Biology* **395,** 1063–1078.

LEWIS JW, SZUNDI I, KAZMI MA, SAKMAR TP & KLIGER DS (2004). Time-resolved photointermediate changes in rhodopsin glutamic acid 181 mutants. *Biochemistry* **43,** 12614–12621.

LEWIS JW, SZUNDI I, KAZMI MA, SAKMAR TP & KLIGER DS (2006). Proton movement and photointermediate kinetics in rhodopsin mutants. *Biochemistry* **45,** 5430–5439.

LI T, SNYDER WK, OLSSON JE & DRYJA TP (1996). Transgenic mice carrying the dominant rhodopsin mutation P347S: evidence for defective vectorial transport of rhodopsin to the outer segments. *Proceedings of the National Academy of Sciences U.S.A.* **93,** 14176–14181.

LIU J, LIU MY, NGUYEN JB, BHAGAT A, MOONEY V & YAN ECY (2011). Thermal properties of rhodopsin: Insight into the molecular mechanism of dim-light vision. *Journal of Biological Chemistry* **286,** 27622–27629.

LIU MY, LIU J, MEHROTRA D, LIU Y, GUO Y, BALDERA-AGUAYO PA, MOONEY VL, NOUR AM & YAN ECY (2013). Thermal stability of rhodopsin and progression of retinitis pigmentosa: comparison of S186W and D190N rhodopsin mutants. *Journal of Biological Chemistry* **288,** 17698–17712.

LÜDEKE S, BECK M, YAN ECY, SAKMAR TP, SIEBERT F & VOGEL R (2005). The role of Glu181 in the photoactivation of rhodopsin. *Journal of Molecular Biology* **353,** 345–356.

MATIAS-FLORENTINO M, AYALA-RAMIREZ R, GRAUE-WIECHERS F & ZENTENO JC (2009). Molecular screening of rhodopsin and peripherin/RDS genes in Mexican families with autosomal dominant retinitis pigmentosa. *Current Eye Research* **34,** 1050–1056.

MCKIBBIN C, TOYE AM, REEVES PJ, KHORANA HG, EDWARDS PC, VILLA C & BOOTH PJ (2007). Opsin stability and folding: The role of Cys185 and abnormal disulfide bond formation in the intradiscal domain. *Journal of Molecular Biology* **374,** 1309–1318.

MIN KC, ZVYAGA TA, CYPESS AM & SAKMAR TP (1993). Characterization of mutant rhodopsins responsible for autosomal dominant retinitis pigmentosa. Mutations on the cytoplasmic surface affect transducin activation. *Journal of Biological Chemistry* **268,** 9400–9404.

NATOCHIN M, GASIMOV KG, MOUSSAIF M & ARTEMYEV NO (2003). Rhodopsin Determinants for Transducin Activation: A gain-of-function approach. *Journal of Biological Chemistry* **278,** 37574–37581.

OLSSON JE, GORDON JW, PAWLYK BS, ROOF D, HAYES A, MOLDAY RS, MUKAI S, COWLEY GS, BERSON EL & DRYJA TP (1992). Transgenic mice with a rhodopsin mutation (Pro23His): a mouse model of autosomal dominant retinitis pigmentosa. *Neuron* **9,** 815–830.

PIECHNICK R, RITTER E & HILDEBRAND PW (2012). Effect of channel mutations on the uptake and release of the retinal ligand in opsin. *Proceedings of the National Academy of Sciences U.S.A.* **109,** 5247-5252**.**

RAO VR, COHEN GB & OPRIAN DD (1994). Rhodopsin mutation G90D and a molecular mechanism for congenital night blindness. *Nature* **367,** 639–642.

ROBINSON PR, COHEN GB, ZHUKOVSKY EA & OPRIAN DD (1992). Constitutively active mutants of rhodopsin. *Neuron* **9,** 719–725.

ROSENFELD PJ, HAHN LB, SANDBERG MA, DRYJA TP & BERSON EL (1995). Low incidence of retinitis pigmentosa among heterozygous carriers of a specific rhodopsin splice site mutation. *Investigative Ophthalmology & Visual Science* **36,** 2186–2192.

SAKMAR TP, FRANKE RR & KHORANA HG (1989). Glutamic acid-113 serves as the retinylidene Schiff base counterion in bovine rhodopsin. *Proceedings of the National Academy of Sciences U.S.A.* **86,** 8309–8313.

SCOTT K, SIEVING PA & BINGHAM E (1993). Rhodopsin mutations associated with autosomal-dominant retinitis-pigmentosa. *American Journal of Human Genetics* **53**, 147.

SHI W, OSAWA S, DICKERSON CD & WEISS ER (1995). Rhodopsin mutants discriminate sites important for the activation of rhodopsin kinase and $G_t$. *Journal of Biological Chemistry* **270,** 2112–2119.

SINGHAL A, OSTERMAIER MK, VISHNIVETSKIY SA, PANNEELS V, HOMAN KT, TESMER JJG, VEPRINTSEV D, DEUPI X, GUREVICH VV, SCHERTLER GFX & STANDFUSS J (2013). Insights into congenital stationary night blindness based on the structure of G90D rhodopsin. *Nature Publishing Group* **14,** 520–526.

SUNG CH, DAVENPORT CM & NATHANS J (1993*)*. Rhodopsin mutations responsible for autosomal dominant retinitis pigmentosa. Clustering of functional classes along the

polypeptide chain. *Journal of Biological Chemistry* **268,** 26645–26649.

SUNG CH, SCHNEIDER BG, AGARWAL N, PAPERMASTER DS & NATHANS J (1991). Functional heterogeneity of mutant rhodopsins responsible for autosomal dominant retinitis pigmentosa. *Proceedings of the National Academy of Sciences U.S.A.* **88,** 8840–8844.

TOLEDO D, RAMON E, AGUILÀ M, CORDOMÍ A, PÉREZ JJ, MENDES HF, CHEETHAM ME & GARRIGA P (2011). Molecular mechanisms of disease for mutations at Gly-90 in rhodopsin. *Journal of Biological Chemistry* **286,** 39993–40001.

VAITHINATHAN R, BERSON EL & DRYJA TP (1994). Further screening of the rhodopsin gene in patients with autosomal dominant retinitis pigmentosa. *Genomics* **21,** 461–463.

VINCENT AL, CARROLL J, FISHMAN GA, SAUER A, SHARP D, SUMMERFELT P, WILLIAMS V, DUBIS AM, KOHL S & WONG F (2013). Rhodopsin F45L allele does not cause Autosomal Dominant Retinitis Pigmentosa in a large Caucasian family. *Translational Vision Science and Technology* **2,** 4.

WEITZ CJ & NATHANS J (1992). Histidine residues regulate the transition of photoexcited rhodopsin to its active conformation, metarhodopsin II. *Neuron* **8,** 465–472.

WEITZ CJ & NATHANS J (1993). Rhodopsin activation: effects of the metarhodopsin I-metarhodopsin II equilibrium of neutralization or introduction of charged amino acids within putative transmembrane regions. *Biochemistry* **32**, 14176-14182.

YAMASHITA T, TERAKITA A & SHICHIDA Y (2000). Distinct roles of the second and third cytoplasmic loops of bovine rhodopsin in G protein activation. *Journal of Biological Chemistry* **275,** 34272–34279.

YAN E, EPPS J, LEWIS JW & SZUNDI I (2007). Photointermediates of the rhodopsin S186A mutant as a probe of the hydrogen-bond network in the chromophore pocket and the mechanism of counterion switch. *The Journal of Physical Chemistry C* **111,** 8843-8848.

YAN ECY, KAZMI MA, DE S, CHANG BSW, SEIBERT C, MARIN EP, MATHIES RA & SAKMAR TP (2002). Function of extracellular loop 2 in rhodopsin: glutamic acid 181 modulates stability and absorption wavelength of M etarhodopsin II. *Biochemistry* **41,** 3620–3627.

ZHANG L, SPORTS CD, OSAWA S & WEISS ER (1997). Rhodopsin phosphorylation sites and their role in arrestin binding. *Journal of Biological Chemistry* **272,** 14762–14768.

ZHANG N, KOLESNIKOV AV, JASTRZEBSKA B, MUSTAFI D, SAWADA O, MAEDA T, GENOUD C, ENGEL A, KEFALOV VJ & PALCZEWSKI K (2012). Autosomal recessive retinitis pigmentosa E150K opsin mice exhibit photoreceptor disorganization. *Journal of Clinical Investigation* **123,** 121–137.

ZHAO K, XIONG S, WANG L & CUI Y (2001). Novel rhodopsin mutation in a Chinese family with autosomal dominant retinitis pigmentosa. *Ophthalmic Genetics* **22,** 155–

162.

ZHU L, IMANISHI Y, FILIPEK S, ALEKSEEV A, JASTRZEBSKA B, SUN W, SAPERSTEIN DA & PALCZEWSKI K (2006). Autosomal Recessive Retinitis Pigmentosa and E150K Mutation in the Opsin Gene. *Journal of Biological Chemistry* **281,** 22289–22298.