Evolution of the Synapse

Baktash Babadi

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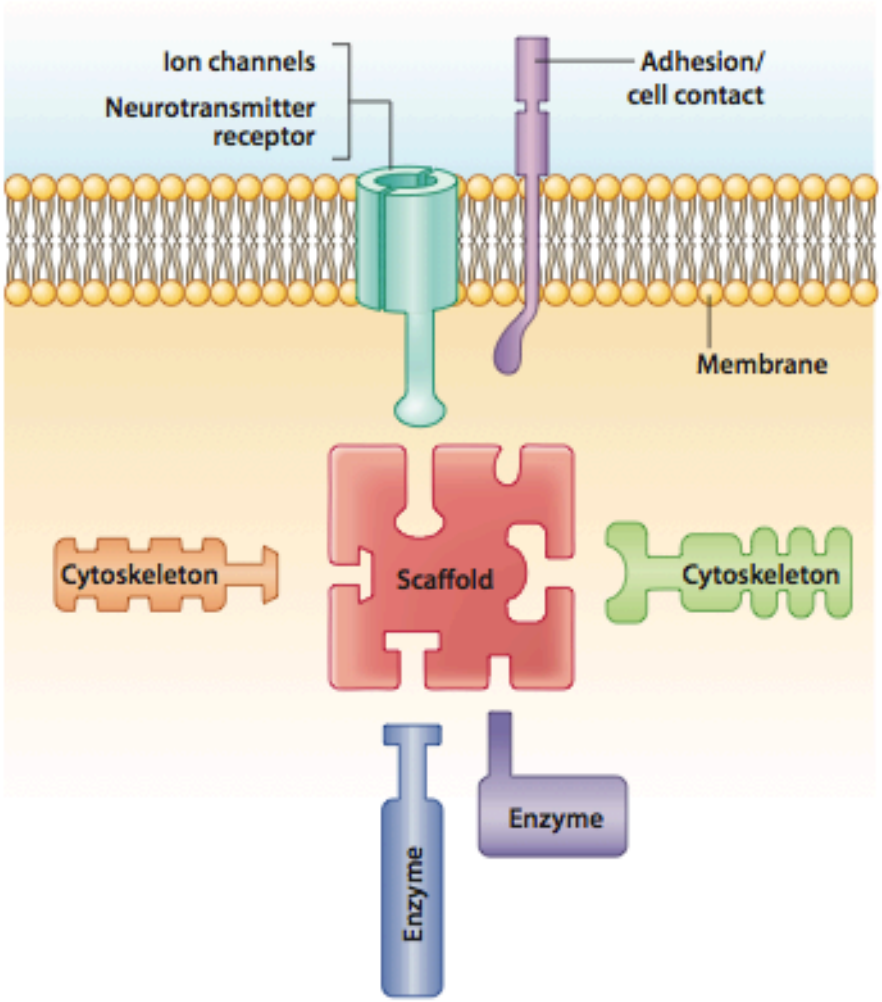
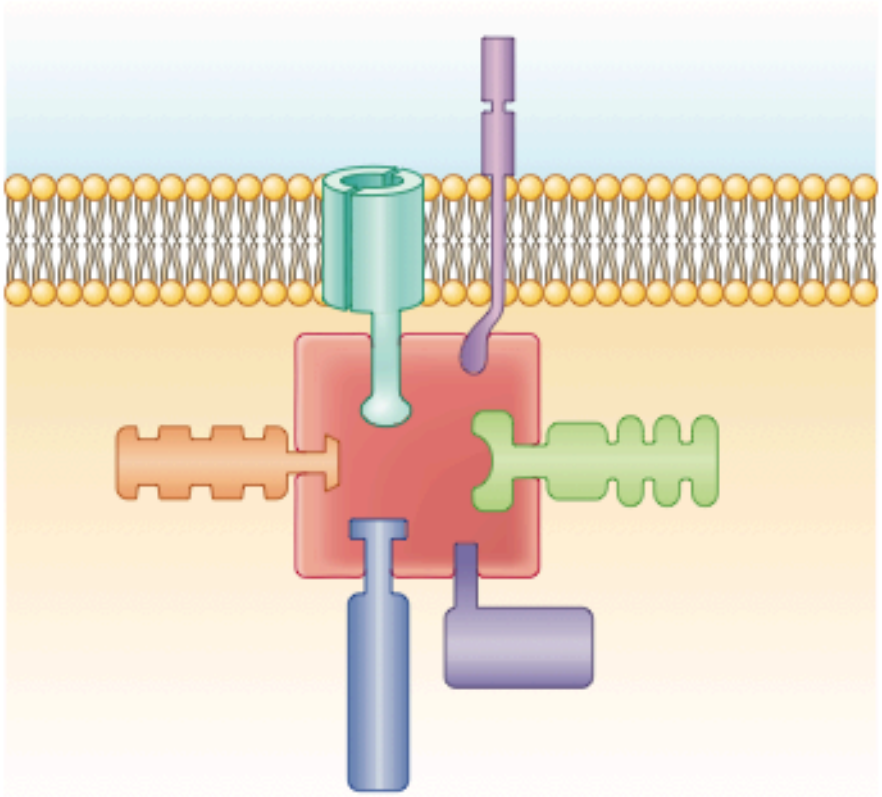
Synaptic multi-protein complex





Components aggregate to form a macromolecular structure tethered to the cell membrane

The Synaptic Proteome

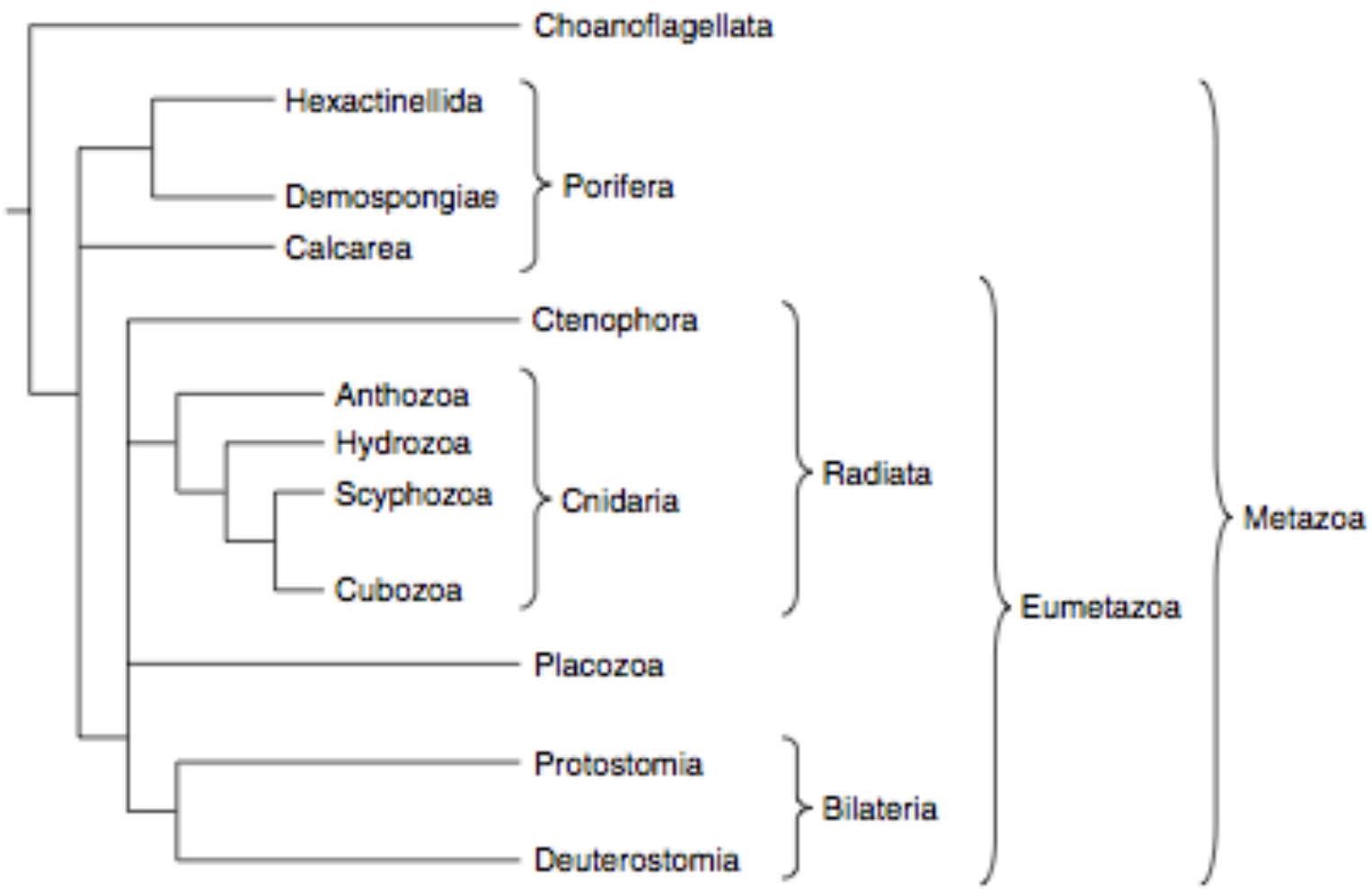
- Postsynaptic: ~1500 proteins
- Presynaptic : Hundreds of proteins

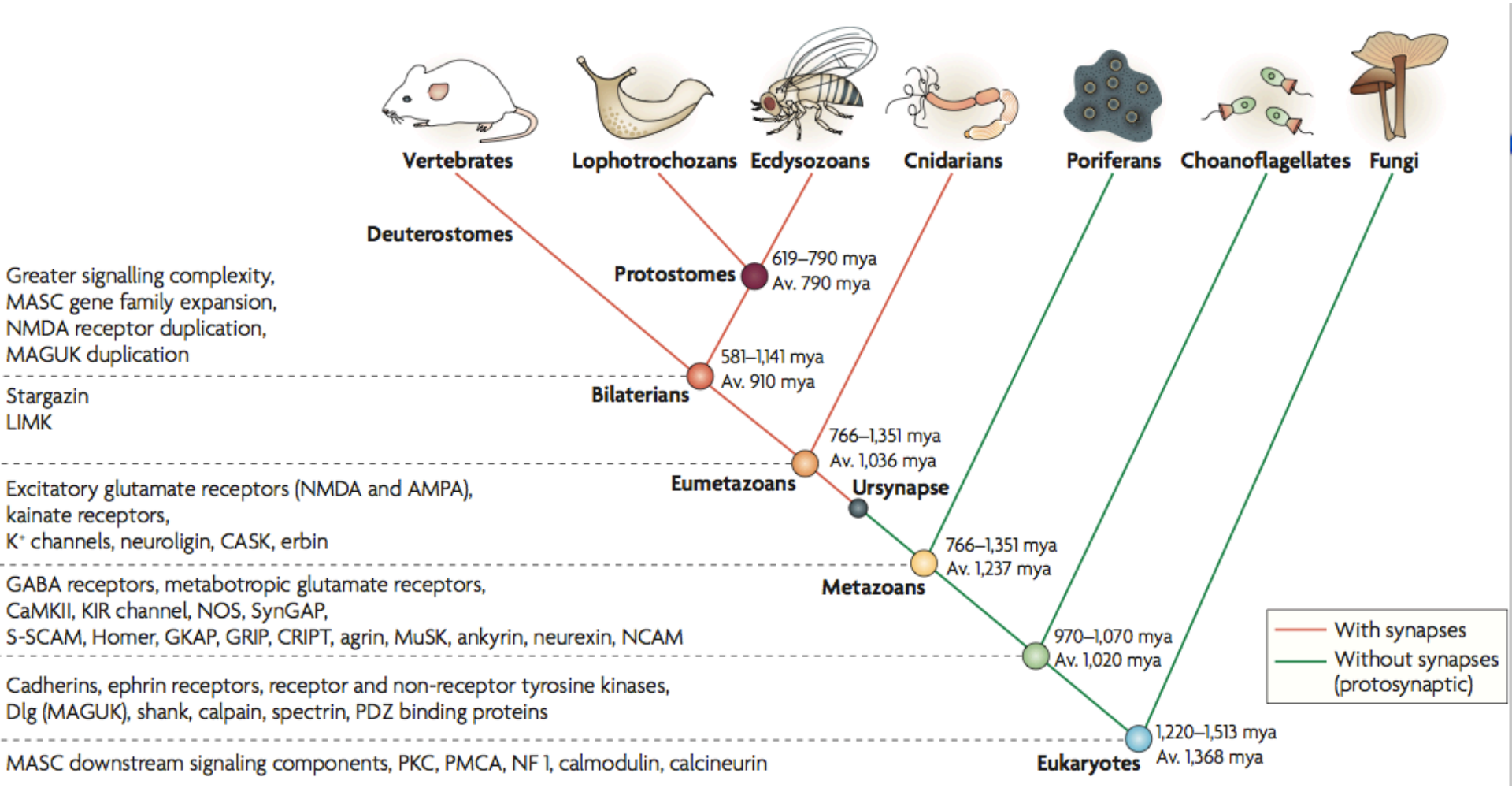
S1 | **Protein classes in mouse PSD and MASC**

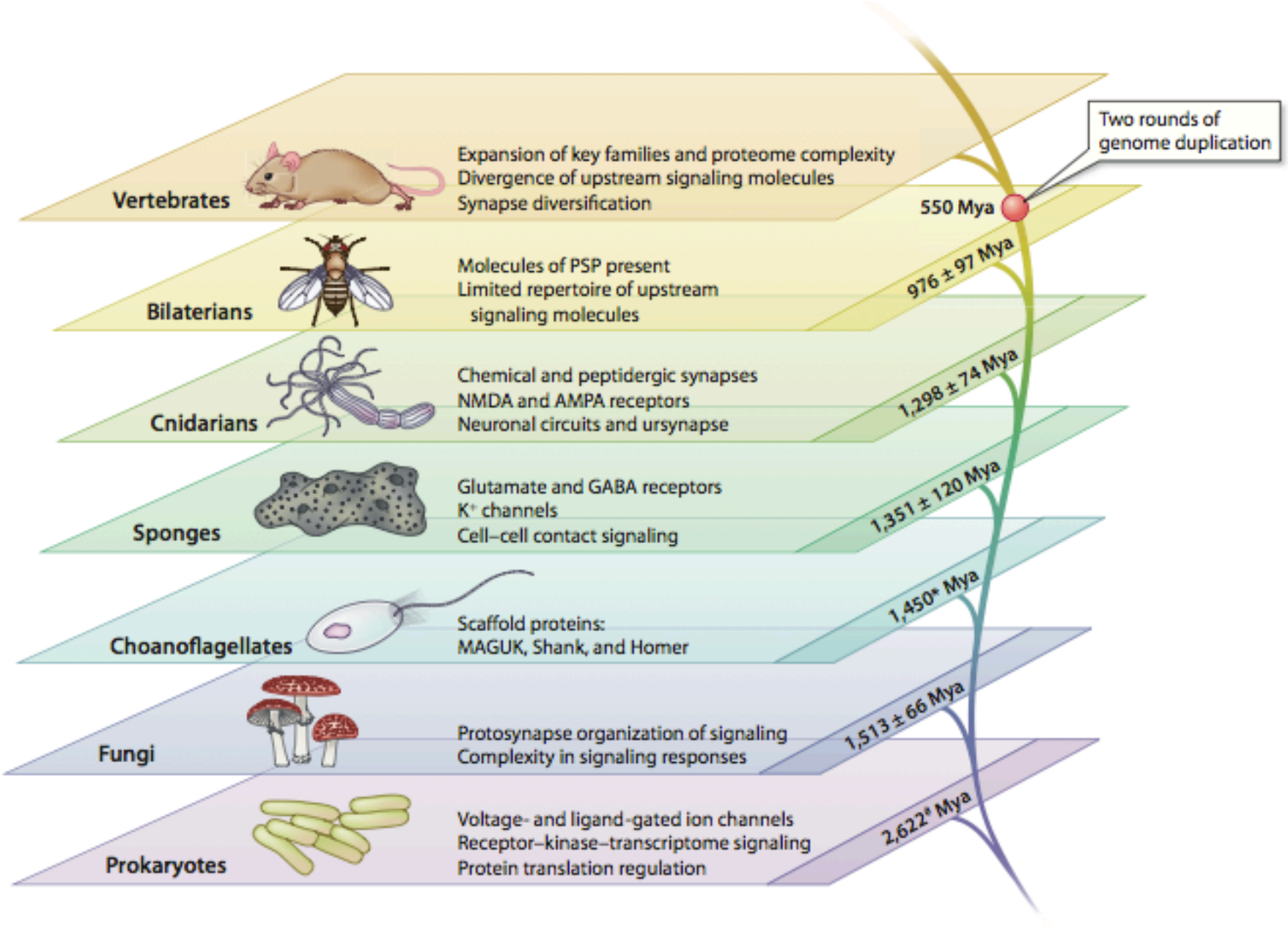
	%PSD	%MASC
Channels and receptors	7	6
MAGUKs/adaptors/scaffolders	5	11
Kinases	4	12
Protein phosphatases	2	4
G-proteins and modulators	7	10
Signalling molecules and enzymes	25	21
Transcription and translation	11	3
Cell adhesion and cytoskeletal	14	19
Synaptic vesicles/protein transport	14	12
Uncharacterized/novel	10	2
Other	3	0
Total number of proteins	1124	186

- Protosynapse → Synaptic components present before the emergence of synapses (Yeast, Sponge)
- Primitive synapse → First neural nets (Cnidarians with radial symmetry)

Animal kingdom




Vertebrates
Lophotrochozans
Ecdysozoans
Cnidarians
Poriferans
Choanoflagellates
Fungi
Deuterostomes
Protostomes
619–790 mya
Av. 790 mya
581–1,141 mya
Av. 910 mya
Bilaterians
766–1,351 mya
Av. 1,036 mya
Eumetazoans
Ursynapse
766–1,351 mya
Av. 1,237 mya
Metazoans
970–1,070 mya
Av. 1,020 mya
1,220–1,513 mya
Av. 1,368 mya
Eukaryotes
With synapses
Without synapses
(protosynaptic)
Greater signalling complexity,
MASC gene family expansion,
NMDA receptor duplication,
MAGUK duplication
Stargazin
LIMK
Excitatory glutamate receptors (NMDA and AMPA),
kainate receptors,
K+ channels, neuroligin, CASK, erbin
GABA receptors, metabotropic glutamate receptors,
CaMKII, KIR channel, NOS, SynGAP,
S-SCAM, Homer, GKAP, GRIP, CRIPT, agrin, MuSK, ankyrin, neurexin, NCAM
Cadherins, ephrin receptors, receptor and non-receptor tyrosine kinases,
Dlg (MAGUK), shank, calpain, spectrin, PDZ binding proteins
MASC downstream signaling components, PKC, PMCA, NF 1, calmodulin, calcineurin


Vertebrates
Expansion of key families and proteome complexity
Divergence of upstream signaling molecules
Synapse diversification
Two rounds of genome duplication
550 Mya
Bilaterians
Molecules of PSP present
Limited repertoire of upstream signaling molecules
976 ± 97 Mya
Cnidarians
Chemical and peptidergic synapses
NMDA and AMPA receptors
Neuronal circuits and ursynapse
1,298 ± 74 Mya
Sponges
Glutamate and GABA receptors
K+ channels
Cell–cell contact signaling
1,351 ± 120 Mya
Choanoflagellates
Scaffold proteins:
MAGUK, Shank, and Homer
1,450* Mya
Fungi
Protosynapse organization of signaling
Complexity in signaling responses
1,513 ± 66 Mya
Prokaryotes
Voltage- and ligand-gated ion channels
Receptor–kinase–transcriptome signaling
Protein translation regulation
2,622* Mya

Protosynapse

Table 1 | **The origin and ancestral functions of protosynaptic proteins**

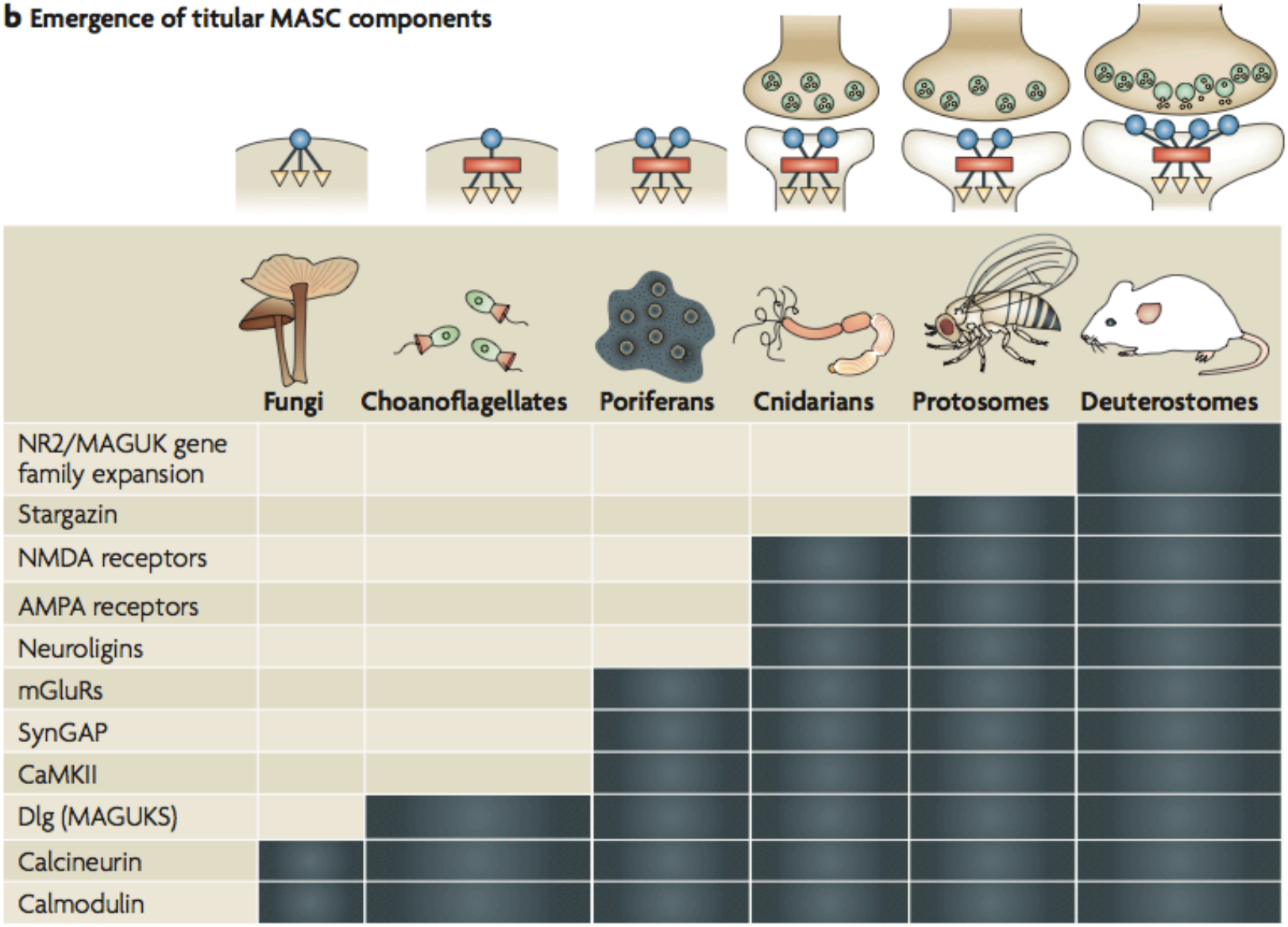
Molecule	Clade of origin	Organism reported	Ancestral function
PKA	Fungi	*S. cerevisiae*[16]	Nutrient induced cell proliferation[106]
NF1	Fungi	*S. cerevisiae*[16]	Stress response[107]
Calmodulin	Fungi	*S. cerevisiae*[16]	Ca^{2+} dependant stress response[18]
Calcineurin	Fungi	*S. cerevisiae*[16]	Ca^{2+} dependant stress response[108]
ERK2	Fungi	*S. cerevisiae*[16]	Pheromone induced cell proliferation[109]
GNB5	Fungi	*S. cerevisiae*[16]	Pheromone induced signalling[110]
SNAP-25	Fungi	*S. cerevisiae*[111]	Vacuolar morphogenesis and trafficking[111]
Syntaxin	Fungi	*S. cerevisiae*[16]	Vacuolar morphogenesis and trafficking[111]
TRP channels	Fungi	*S. cerevisiae*[112]	Osmolarity stress response[112]
Cadherin	Choanoflagellata	*M. brevicollis*[24]	Unknown, co-localizes with actin filaments at the apical collar[29]
SRC kinase	Choanoflagellata	*M. brevicollis*[113]	Regulation of cell proliferation[24]
RAF kinase	Choanoflagellata	*M. brevicollis*[24]	Unknown
Ephrin receptors	Choanoflagellata	*M. brevicollis*[26]	Unknown
Calpain	Choanoflagellata	*M. brevicollis*[114]	Unknown
Spectrin	Choanoflagellata	*M. brevicollis*[115]	Unknown
Dlg (MAGUK)	Choanoflagellata	*M. brevicollis*[13,116]	Unknown
Shank	Choanoflagellata	*M. brevicollis*[13,116]	Unknown
Agrin	Porifera	*O. carmela*[31]	Unknown
MuSK	Porifera	*O. carmela*[31]	Unknown
Ankyrin	Porifera	*O. carmela*[31]	Unknown
Neurexin	Porifera	*O. carmela*[31]	Unknown
NCAM	Porifera	*O. carmela*[31]	Unknown
GABA receptors	Porifera	*A. queenslandica*[13]	Unknown
mGluR receptors	Porifera	*A. queenslandica*[13]	Unknown, activity modulates Ca^{2+} influx[35]
KIR channels	Porifera	*A. queenslandica*[13]	Unknown
CaMKII	Porifera	*A. queenslandica*[13]	Unknown
NOS	Porifera	*A. queenslandica*[13]	Unknown
SynGAP	Porifera	*A. queenslandica*[13]	Unknown
S-SCAM	Porifera	*A. queenslandica*[13]	Unknown, located in epithelial cells[117]
Homer	Porifera	*A. queenslandica*[13]	Unknown, located in epithelial cells[13]
GKAP	Porifera	*A. queenslandica*[13]	Unknown, located in epithelial cells[13]
GRIP	Porifera	*A. queenslandica*[13]	Unknown, located in epithelial cells[13]
CRIPT	Porifera	*A. queenslandica*[13]	Unknown, located in epithelial cells[13]

Primitive Synapse

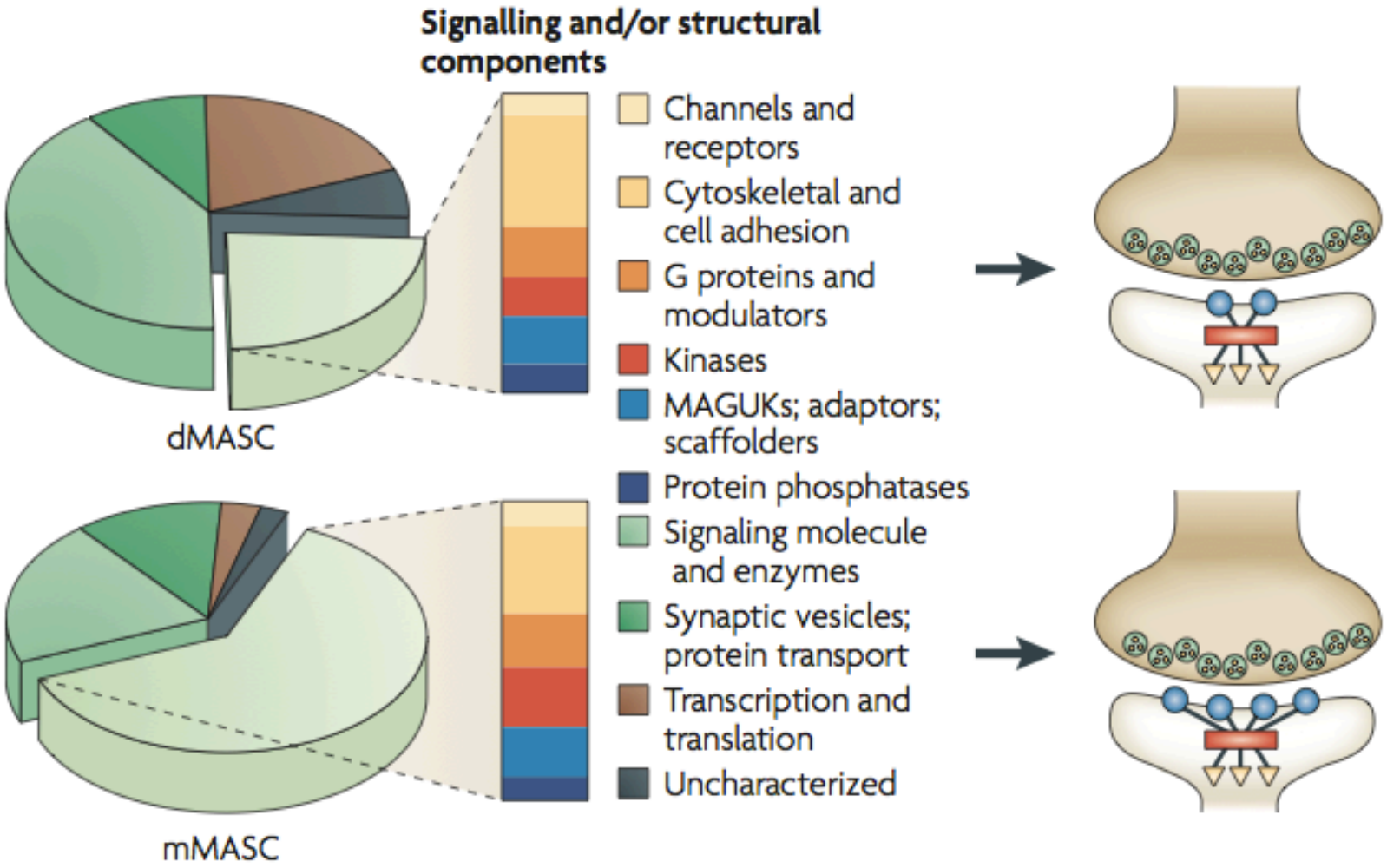
Table 2 | **Synaptic proteins present in early organisms with a nervous system**

Molecule	Clade idenified	Organism	Synaptic function
NMDA receptors	Cnidaria	*N. vectensis*[13]	Induction of synaptic plasticity[118]
AMPA receptors	Cnidaria	*N. vectensis*[13]	Fast synaptic transmission and plasticity[119]
Kainate receptors	Cnidaria	*N. vectensis*[13]	Modulation of synaptic transmission and plasticity[120]
Shaker channel	Cnidaria	*N. vectensis*[13]	Synaptic homeostasis[121]
Neuroligin	Cnidaria	*N. vectensis*[13]	Synapse formation[42]
Erbin	Cnidaria	*N. vectensis*[13]	Modulation of voltage dependant calcium channels[122]
CASK	Cnidaria	*N. vectensis*[13]	Regulation of neurotransmitter release[123]

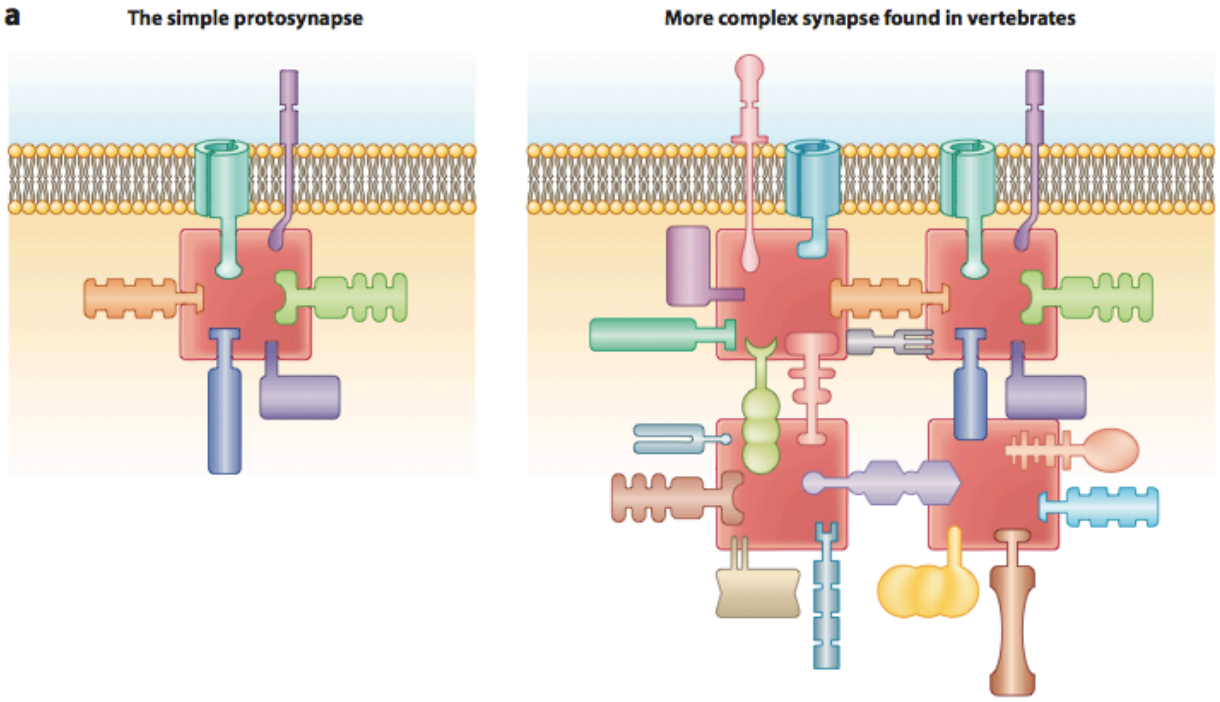
Emergence of Synaptic components

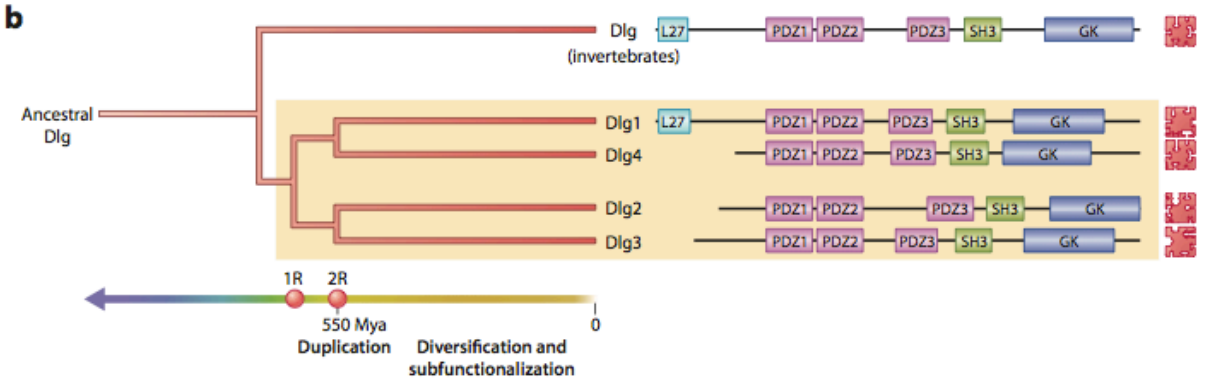


D. Melanogaster vs. Mouse

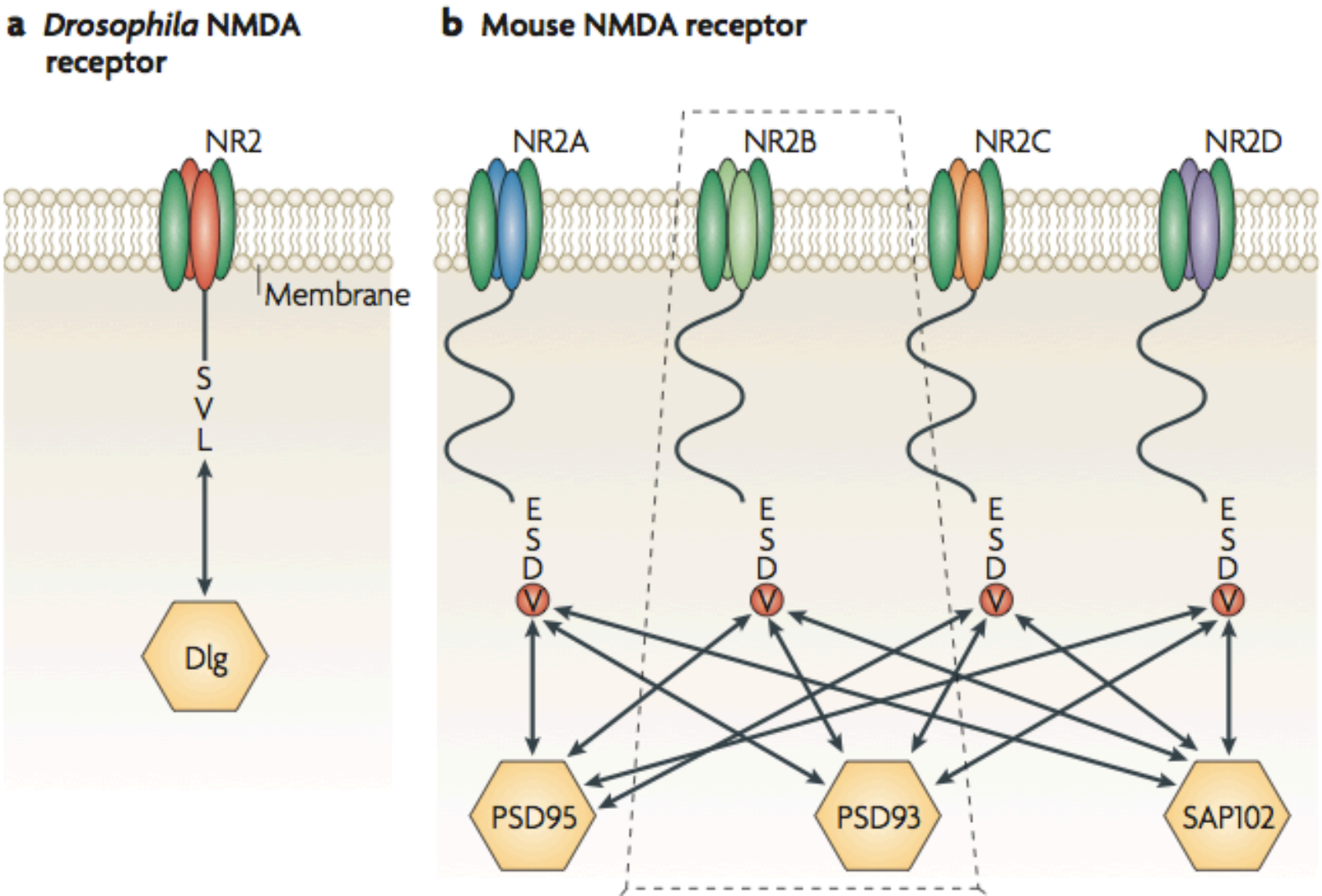


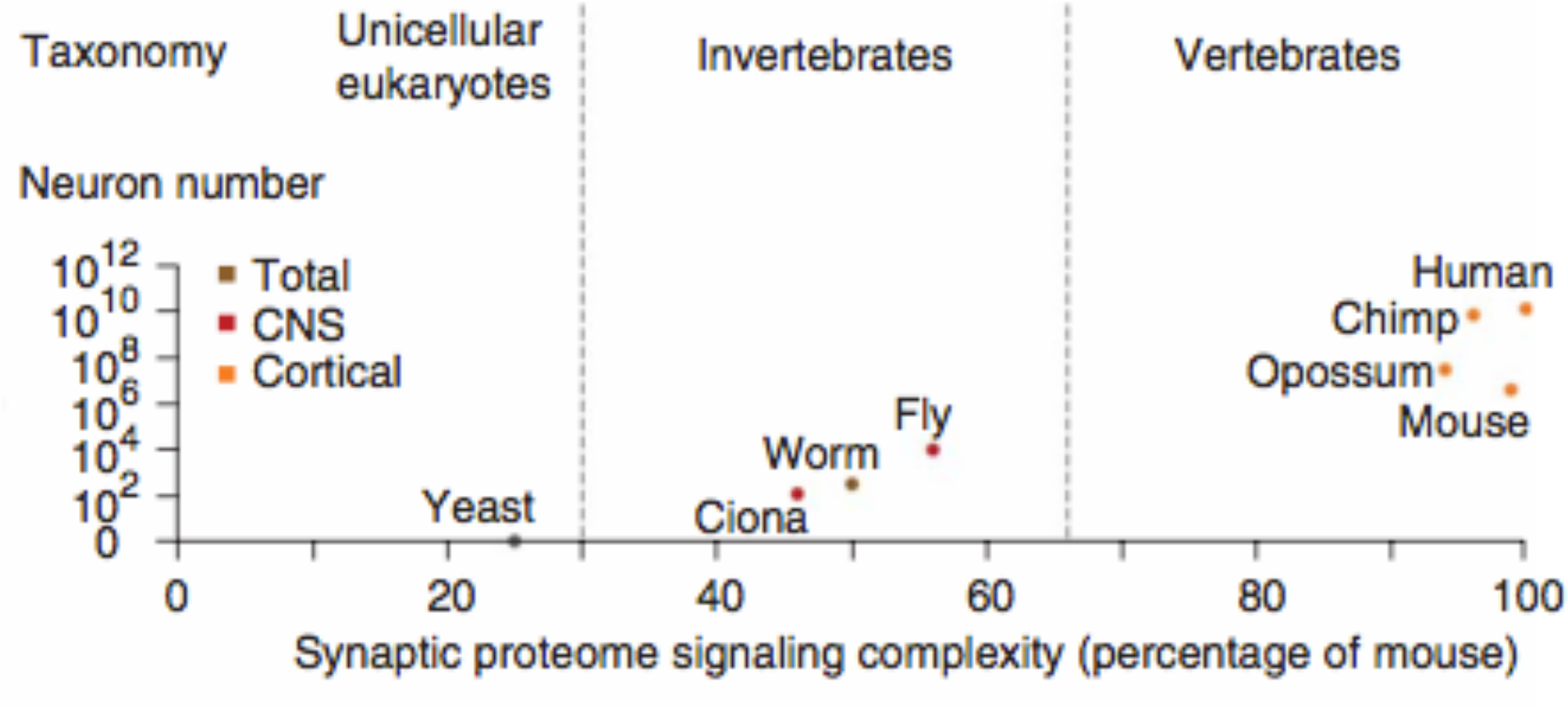
Gene duplication events





Gene duplications in Chordates



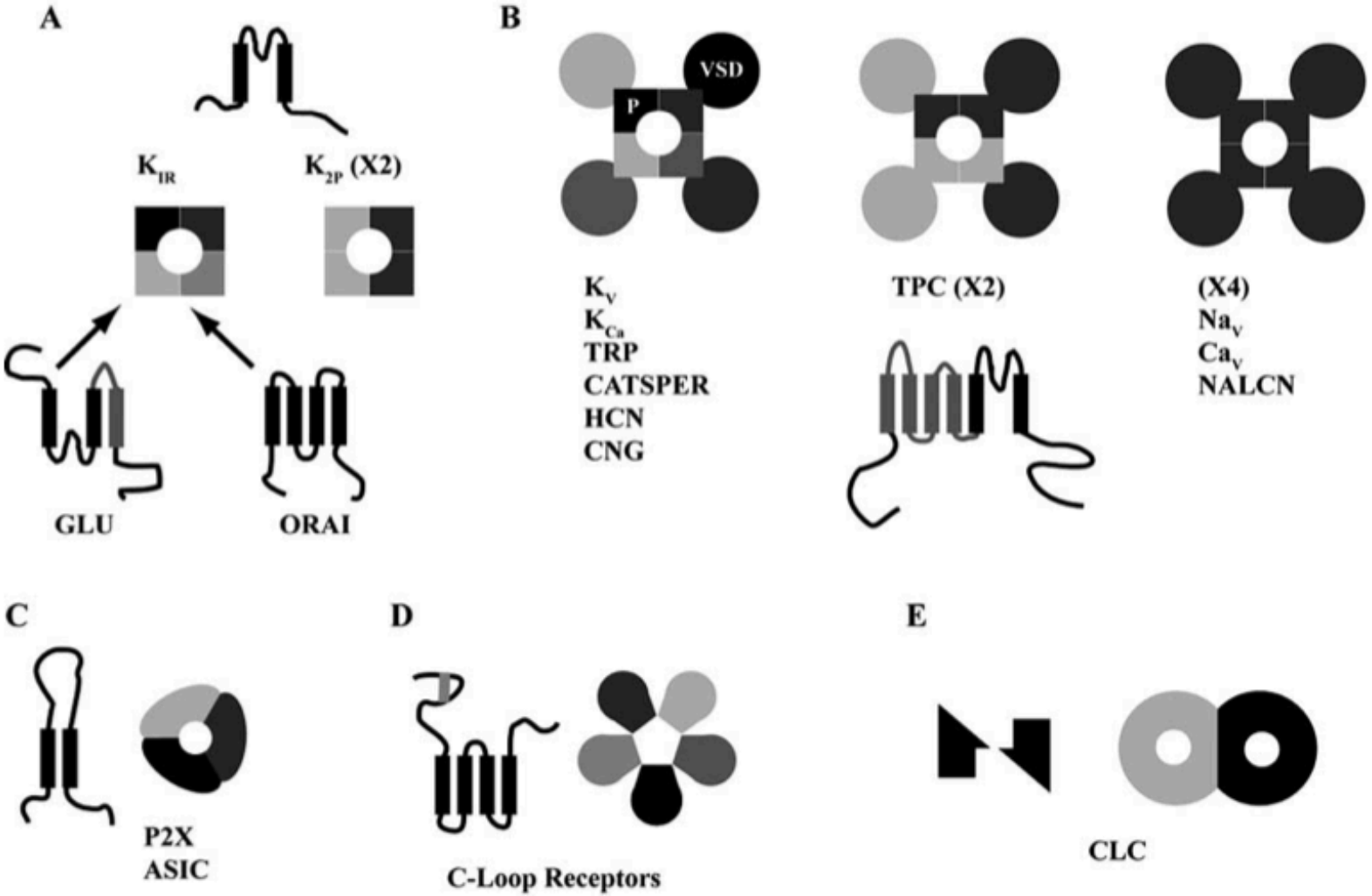

Taxonomy
Unicellular eukaryotes
Invertebrates
Vertebrates
Neuron number
10^{12}
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
0
Total
CNS
Cortical
Yeast
Ciona
Worm
Fly
Human
Chimp
Opossum
Mouse
0
20
40
60
80
100
Synaptic proteome signaling complexity (percentage of mouse)

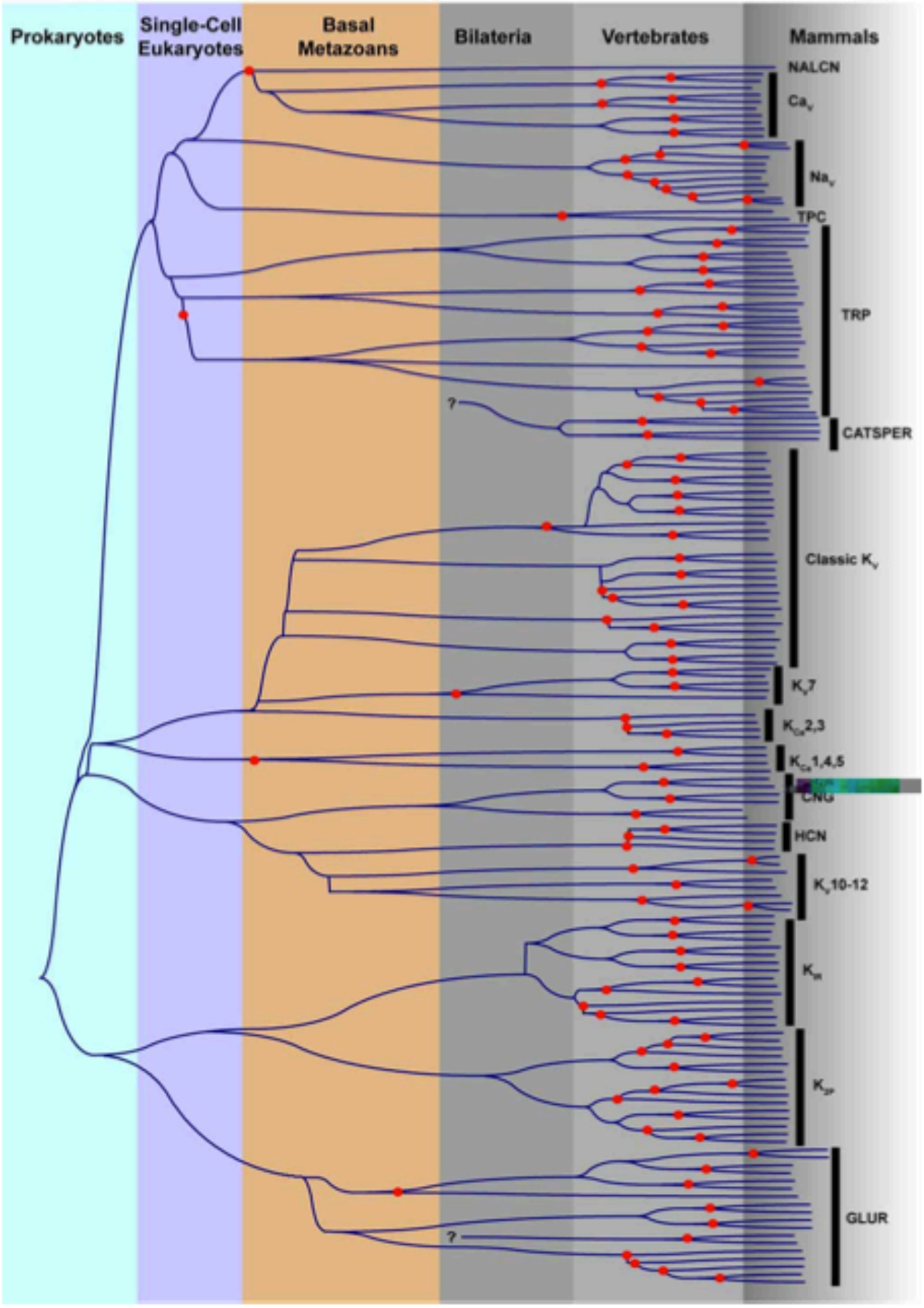
Phylogeny of Ligand gated channels

- Cyc-loop receptors
  - GABA A
  - GlyR
  - 5-HTR
  - nAchR
- iGlu receptors
  - AMPA
  - Kynate
  - NMDA
  - Orphan

- ATP gated channels

Ion channel super family




Prokaryotes
Single-Cell Eukaryotes
Basal Metazoans
Bilateria
Vertebrates
Mammals
NALCN
Ca_v
Na_v
TPC
TRP
?
CATSPER
Classic K_v
K_v7
$K_{Ca}2,3$
$K_{Ca}1,4,5$
CNG
HCN
$K_v10\text{-}12$
K_{sr}
K_{2P}
GLUR
?