ADDITIONAL FILE 2: Sequence analyses

Table S2.1: Flamingo/Celsr/Stan sequence identity matrix. Obtained using bioedit software.

Seq->	MmCelsr1	DrCelsr1b	DrCelsr1a	MmCelsr2	DrCelsr2	MmCelsr3	DrCelsr3
MmCelsr1	ID	0,596	0,609	0,539	0,52	0,431	0,262
DrCelsr1b	0,596	ID	0,702	0,516	0,528	0,427	0,267
DrCelsr1a	0,609	0,702	ID	0,522	0,535	0,431	0,264
MmCelsr2	0,539	0,516	0,522	ID	0,605	0,442	0,269
DrCelsr2	0,52	0,528	0,535	0,605	ID	0,43	0,257
MmCelsr3	0,431	0,427	0,431	0,442	0,43	ID	0,351
DrCelsr3	0,262	0,267	0,264	0,269	0,257	0,351	ID
DmStan	0,29	0,287	0,285	0,279	0,286	0,284	0,161
ChFmi	0,235	0,241	0,248	0,234	0,25	0,207	0,127
TaCelsr	0,264	0,269	0,271	0,257	0,255	0,25	0,137
OcFmi	0,217	0,215	0,213	0,212	0,213	0,203	0,116
OlFmi	0,227	0,219	0,225	0,216	0,222	0,198	0,102
ScFmi	0,184	0,181	0,178	0,194	0,179	0,173	0,099
AqCelsr3L	0,127	0,129	0,136	0,131	0,128	0,122	0,092

Seq->	DmStan	ChFmi	TaCelsr	OcFmi	OlFmi	ScFmi	AqCelsr3L
MmCelsr1	0,29	0,235	0,264	0,217	0,227	0,184	0,127
DrCelsr1b	0,287	0,241	0,269	0,215	0,219	0,181	0,129
DrCelsr1a	0,285	0,248	0,271	0,213	0,225	0,178	0,136
MmCelsr2	0,279	0,234	0,257	0,212	0,216	0,194	0,131
DrCelsr2	0,286	0,25	0,255	0,213	0,222	0,179	0,128
MmCelsr3	0,284	0,207	0,25	0,203	0,198	0,173	0,122
DrCelsr3	0,161	0,127	0,137	0,116	0,102	0,099	0,092
DmStan	ID	0,192	0,225	0,181	0,184	0,151	0,113
ChFmi	0,192	ID	0,214	0,185	0,197	0,159	0,117
TaCelsr	0,225	0,214	ID	0,202	0,199	0,17	0,126
OcFmi	0,181	0,185	0,202	ID	0,545	0,197	0,132
OlFmi	0,184	0,197	0,199	0,545	ID	0,196	0,126
ScFmi	0,151	0,159	0,17	0,197	0,196	ID	0,127
AqCelsr3L	0,113	0,117	0,126	0,132	0,126	0,127	ID

Abbreviations. Vertebrate: Dr, *Danio rerio* and Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Cnidaria: Ch, *Clytia hemisphaerica.* Placozoa: Ta, *Trichoplax adhaerens*. Porifera: Aq, *Amphimedon queenslandica*; *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; Sc, *Sycon ciliatum*.

Table S2.2: Fuzzy sequence identity matrix. Obtained using bioedit software.

Seq->	DrFuz	MmFuz	DmFy	ChFy	TaFy	OcFuz	OlFuz
DrFuz	ID	0,436	0,219	0,245	0,23	0,272	0,248
MmFuz	0,436	ID	0,216	0,244	0,201	0,247	0,224
DmFy	0,219	0,216	ID	0,166	0,168	0,214	0,22
ChFy	0,245	0,244	0,166	ID	0,162	0,18	0,161
TaFy	0,23	0,201	0,168	0,162	ID	0,185	0,181
OcFuz	0,272	0,247	0,214	0,18	0,185	ID	0,587
OlFuz	0,248	0,224	0,22	0,161	0,181	0,587	ID
OspFuz	0,082	0,075	0,071	0,097	0,065	0,144	0,174
ScFuz	0,262	0,273	0,195	0,173	0,228	0,309	0,259
AqFuz	0,211	0,219	0,168	0,182	0,162	0,222	0,199
EmFuz	0,275	0,275	0,209	0,18	0,262	0,291	0,263
MlFy	0,153	0,14	0,132	0,116	0,146	0,168	0,182
SrFy	0,195	0,215	0,158	0,146	0,144	0,196	0,19

Seq->	OspFuz	ScFuz	AqFuz	EmFuz	MlFy	SrFy
DrFuz	0,082	0,262	0,211	0,275	0,153	0,195
MmFuz	0,075	0,273	0,219	0,275	0,14	0,215
DmFy	0,071	0,195	0,168	0,209	0,132	0,158
ChFy	0,097	0,173	0,182	0,18	0,116	0,146
TaFy	0,065	0,228	0,162	0,262	0,146	0,144
OcFuz	0,144	0,309	0,222	0,291	0,168	0,196
OlFuz	0,174	0,259	0,199	0,263	0,182	0,19
OspFuz	ID	0,09	0,116	0,077	0,055	0,084
ScFuz	0,09	ID	0,248	0,341	0,171	0,224
AqFuz	0,116	0,248	ID	0,308	0,11	0,194
EmFuz	0,077	0,341	0,308	ID	0,152	0,193
MlFy	0,055	0,171	0,11	0,152	ID	0,099
SrFy	0,084	0,224	0,194	0,193	0,099	ID

Abbreviations. Vertebrate: Dr, *Danio rerio* and Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Cnidaria: Ch, *Clytia hemisphaerica.* Placozoa: Ta, *Trichoplax adhaerens*. Porifera: Aq, *Amphimedon queenslandica*; Em, *Ephydatia muelleri*; *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; *Osp, Oscarella sp.*; Sc, *Sycon ciliatum*. Ctenophora: Ml, *Mnemiopsis leidyi*. Choanoflagellata: Sr, *Salpingoeca rosetta*.

Table S2.3: Inturned sequence identity matrix. Obtained using bioedit software.

Seq->	MmIntu	DrIntu	DmIn	SpIn	LcIn	SmIn	ChIn
MmIntu	ID	0,477	0,161	0,328	0,572	0,183	0,19
DrIntu	0,477	ID	0,161	0,321	0,512	0,184	0,196
DmIn	0,161	0,161	ID	0,157	0,146	0,119	0,129
SpIn	0,328	0,321	0,157	ID	0,312	0,178	0,183
LcIn	0,572	0,512	0,146	0,312	ID	0,173	0,176
SmIn	0,183	0,184	0,119	0,178	0,173	ID	0,117
ChIn	0,19	0,196	0,129	0,183	0,176	0,117	ID
TaIn	0,172	0,185	0,135	0,174	0,169	0,129	0,152
OspIntu	0,142	0,139	0,081	0,134	0,126	0,109	0,128
OcIntu	0,222	0,233	0,145	0,208	0,21	0,14	0,19
OlIntu	0,211	0,216	0,137	0,185	0,186	0,129	0,18
ScIntu	0,199	0,185	0,123	0,193	0,197	0,125	0,169
EmIntu	0,2	0,174	0,133	0,178	0,17	0,112	0,173
AqIntu	0,179	0,17	0,126	0,163	0,161	0,1	0,152
AvIntu	0,085	0,079	0,057	0,078	0,086	0,069	0,075
OmIntu	0,172	0,167	0,12	0,157	0,171	0,121	0,153
SrInL	0,081	0,096	0,087	0,076	0,07	0,062	0,078

Seq->	TaIn	OspIntu	OcIntu	OlIntu	ScIntu	EmIntu	AqIntu
MmIntu	0,172	0,142	0,222	0,211	0,199	0,2	0,179
DrIntu	0,185	0,139	0,233	0,216	0,185	0,174	0,17
DmIn	0,135	0,081	0,145	0,137	0,123	0,133	0,126
SpIn	0,174	0,134	0,208	0,185	0,193	0,178	0,163
LcIn	0,169	0,126	0,21	0,186	0,197	0,17	0,161
SmIn	0,129	0,109	0,14	0,129	0,125	0,112	0,1
ChIn	0,152	0,128	0,19	0,18	0,169	0,173	0,152
TaIn	ID	0,122	0,163	0,152	0,149	0,145	0,135
OspIntu	0,122	ID	0,384	0,44	0,148	0,124	0,111
OcIntu	0,163	0,384	ID	0,632	0,222	0,183	0,186
OlIntu	0,152	0,44	0,632	ID	0,197	0,177	0,175
ScIntu	0,149	0,148	0,222	0,197	ID	0,178	0,144
EmIntu	0,145	0,124	0,183	0,177	0,178	ID	0,224
AqIntu	0,135	0,111	0,186	0,175	0,144	0,224	ID
AvIntu	0,05	0,232	0,073	0,074	0,072	0,066	0,06
OmIntu	0,12	0,117	0,173	0,159	0,172	0,153	0,146
SrInL	0,073	0,078	0,096	0,092	0,068	0,079	0,083

Seq->	AvIntu	OmIntu	SrInL
MmIntu	0,085	0,172	0,081
DrIntu	0,079	0,167	0,096
DmIn	0,057	0,12	0,087
SpIn	0,078	0,157	0,076
LcIn	0,086	0,171	0,07
SmIn	0,069	0,121	0,062
ChIn	0,075	0,153	0,078
TaIn	0,05	0,12	0,073
OspIntu	0,232	0,117	0,078
OcIntu	0,073	0,173	0,096
OlIntu	0,074	0,159	0,092
ScIntu	0,072	0,172	0,068
EmIntu	0,066	0,153	0,079
AqIntu	0,06	0,146	0,083
AvIntu	ID	0,245	0,037
OmIntu	0,245	ID	0,076
SrInL	0,037	0,076	ID

Abbreviations. Vertebrate: Dr, *Danio rerio;* Lc, Latimeria chalumnae and Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Ambulacraria. Sp, *Strongylocentrotus purpuratus*. Cnidaria: Ch, *Clytia hemisphaerica;* Nv, *Nematostella vectensis.* Placozoa: Ta, *Trichoplax adhaerens*. Porifera: Aq, *Amphimedon queenslandica*; Av, *Aphrocalistes vastus*; Em, *Ephydatia muelleri*; *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; *Om, Oopsacas minuta*; *Osp, Oscarella sp*.; Sc, *Sycon ciliatum*. Ctenophora: Ml, *Mnemiopsis leidyi*. Choanoflagellata: Sr, *Salpingoeca rosetta*.

Table S2.4: Inversin sequence identity matrix. Obtained using bioedit software.

Seq->	MmInvs	DrInvs	HpInvsL	SkInvs	AcInvs	ChDgo	OcInvs1
MmInvs	ID	0,514	0,341	0,359	0,308	0,211	0,281
DrInvs	0,514	ID	0,346	0,356	0,313	0,21	0,291
HpInvsL	0,341	0,346	ID	0,52	0,364	0,211	0,362
SkInvs	0,359	0,356	0,52	ID	0,388	0,228	0,408
AcInvs	0,308	0,313	0,364	0,388	ID	0,182	0,305
ChDgo	0,211	0,21	0,211	0,228	0,182	ID	0,223
OcInvs1	0,281	0,291	0,362	0,408	0,305	0,223	ID
OlInvs1	0,289	0,293	0,364	0,411	0,306	0,221	0,863
OspInvs1	0,283	0,286	0,361	0,408	0,304	0,223	0,808
ScInvs1	0,257	0,277	0,346	0,367	0,287	0,229	0,472
AqInvs1	0,227	0,239	0,29	0,322	0,244	0,217	0,392
EmInvs1	0,242	0,257	0,338	0,354	0,268	0,218	0,425
AvInvs1	0,182	0,175	0,215	0,251	0,176	0,171	0,26
OmInvs1	0,178	0,186	0,224	0,255	0,197	0,182	0,283
OcInvs2	0,165	0,177	0,197	0,208	0,162	0,146	0,212
OlInvs2	0,175	0,191	0,185	0,194	0,158	0,145	0,215
OspInvs2	0,183	0,191	0,188	0,194	0,154	0,138	0,215
ScInvs2	0,158	0,166	0,166	0,183	0,138	0,148	0,183
AqInvs2	0,173	0,179	0,192	0,195	0,16	0,152	0,206
EmInvs2	0,197	0,199	0,188	0,203	0,16	0,175	0,212
AvInvs2	0,154	0,162	0,156	0,171	0,132	0,151	0,177
OmInvs2	0,157	0,168	0,166	0,185	0,143	0,154	0,185
SrInL	0,196	0,196	0,21	0,222	0,177	0,187	0,22

Seq->	Ollnvs1	Ospinvs1	Sclnvs1	Aqlnvs1	Emlnvs1	Avlnvs1	Omlnvs1
Mmlnvs	0,289	0,283	0,257	0,227	0,242	0,182	0,178
Drlnvs	0,293	0,286	0,277	0,239	0,257	0,175	0,186
HplnvsL	0,364	0,361	0,346	0,29	0,338	0,215	0,224
Sklnvs	0,411	0,408	0,367	0,322	0,354	0,251	0,255
Aclnvs	0,306	0,304	0,287	0,244	0,268	0,176	0,197
ChDgo	0,221	0,223	0,229	0,217	0,218	0,171	0,182
Oclnvs1	0,863	0,808	0,472	0,392	0,425	0,26	0,283
Ollnvs1	ID	0,863	0,466	0,391	0,438	0,263	0,286
Ospinvs1	0,863	ID	0,466	0,389	0,427	0,26	0,288
Sclnvs1	0,466	0,466	ID	0,359	0,393	0,25	0,283
Aqlnvs1	0,391	0,389	0,359	ID	0,483	0,282	0,304
Emlnvs1	0,438	0,427	0,393	0,483	ID	0,297	0,295
Avlnvs1	0,263	0,26	0,25	0,282	0,297	ID	0,481
Omlnvs1	0,286	0,288	0,283	0,304	0,295	0,481	ID
Oclnvs2	0,219	0,209	0,206	0,197	0,188	0,175	0,177
Ollnvs2	0,222	0,212	0,198	0,189	0,2	0,173	0,175
Ospinvs2	0,224	0,208	0,198	0,195	0,218	0,172	0,185
Sclnvs2	0,182	0,186	0,188	0,194	0,199	0,16	0,165
Aqlnvs2	0,205	0,2	0,201	0,184	0,205	0,17	0,166
Emlnvs2	0,217	0,211	0,215	0,196	0,197	0,159	0,153
Avlnvs2	0,174	0,174	0,178	0,161	0,162	0,152	0,15
Omlnvs2	0,187	0,183	0,202	0,178	0,191	0,167	0,166
SrInL	0,226	0,221	0,225	0,202	0,227	0,168	0,169

Seq->	OcInvs2	OlInvs2	OspInvs2	ScInvs2	AqInvs2	EmInvs2	AvInvs2
MmInvs	0,165	0,175	0,183	0,158	0,173	0,197	0,154
DrInvs	0,177	0,191	0,191	0,166	0,179	0,199	0,162
HpInvsL	0,197	0,185	0,188	0,166	0,192	0,188	0,156
SkInvs	0,208	0,194	0,194	0,183	0,195	0,203	0,171
AcInvs	0,162	0,158	0,154	0,138	0,16	0,16	0,132
ChDgo	0,146	0,145	0,138	0,148	0,152	0,175	0,151
OcInvs1	0,212	0,215	0,215	0,183	0,206	0,212	0,177
OlInvs1	0,219	0,222	0,224	0,182	0,205	0,217	0,174
OspInvs1	0,209	0,212	0,208	0,186	0,2	0,211	0,174
ScInvs1	0,206	0,198	0,198	0,188	0,201	0,215	0,178
AqInvs1	0,197	0,189	0,195	0,194	0,184	0,196	0,161
EmInvs1	0,188	0,2	0,218	0,199	0,205	0,197	0,162
AvInvs1	0,175	0,173	0,172	0,16	0,17	0,159	0,152
OmInvs1	0,177	0,175	0,185	0,165	0,166	0,153	0,15
OcInvs2	ID	0,656	0,561	0,228	0,253	0,237	0,223
OlInvs2	0,656	ID	0,653	0,211	0,263	0,224	0,214
OspInvs2	0,561	0,653	ID	0,216	0,236	0,206	0,203
ScInvs2	0,228	0,211	0,216	ID	0,232	0,242	0,183
AqInvs2	0,253	0,263	0,236	0,232	ID	0,316	0,254
EmInvs2	0,237	0,224	0,206	0,242	0,316	ID	0,23
AvInvs2	0,223	0,214	0,203	0,183	0,254	0,23	ID
OmInvs2	0,243	0,244	0,225	0,203	0,254	0,248	0,559
SrInL	0,196	0,2	0,184	0,178	0,191	0,201	0,179

Seq->	OmInvs2	SrInL
MmInvs	0,157	0,196
DrInvs	0,168	0,196
HpInvsL	0,166	0,21
SkInvs	0,185	0,222
AcInvs	0,143	0,177
ChDgo	0,154	0,187
OcInvs1	0,185	0,22
OlInvs1	0,187	0,226
OspInvs1	0,183	0,221
ScInvs1	0,202	0,225
AqInvs1	0,178	0,202
EmInvs1	0,191	0,227
AvInvs1	0,167	0,168
OmInvs1	0,166	0,169
OcInvs2	0,243	0,196
OlInvs2	0,244	0,2
OspInvs2	0,225	0,184
ScInvs2	0,203	0,178
AqInvs2	0,254	0,191
EmInvs2	0,248	0,201
AvInvs2	0,559	0,179
OmInvs2	ID	0,182
SrInL	0,182	ID

Abbreviations. Vertebrate: Dr, *Danio rerio* and Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Mollusca: Ac, *Aplysia californica* and Cg, *Crassotrea gigantea*. Ambulacraria: Hp, *Hemicentrotus pulcherrimus*; Sk and *Saccoglossus kowalevskii*. Cnidaria: Ch, *Clytia hemisphaerica.* Porifera: Aq, *Amphimedon queenslandica*; Av, *Aphrocalistes vastus*; Em, *Ephydatia muelleri*; *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; *Om, Oopsacas minuta*; *Osp, Oscarella sp*.; Sc, *Sycon ciliatum*. Choanoflagellata: Sr, *Salpingoeca rosetta*.

Table S2.4: PET family sequence identity matrix. Obtained using bioedit software.

Seq->	MmPkL1	MmPkL2	MmPkL3	DmPk	DmEsn	ChPk	TaPk
MmPkL1	ID	0,484	0,292	0,198	0,249	0,24	0,215
MmPkL2	0,484	ID	0,323	0,193	0,247	0,225	0,19
MmPkL3	0,292	0,323	ID	0,174	0,259	0,255	0,269
DmPk	0,198	0,193	0,174	ID	0,303	0,162	0,127
DmEsn	0,249	0,247	0,259	0,303	ID	0,226	0,211
ChPk	0,24	0,225	0,255	0,162	0,226	ID	0,215
TaPk	0,215	0,19	0,269	0,127	0,211	0,215	ID
MmTes	0,117	0,115	0,188	0,081	0,13	0,144	0,169
DmTes	0,078	0,075	0,118	0,06	0,082	0,099	0,103
ChTes	0,136	0,129	0,196	0,086	0,139	0,152	0,185
OcPkTesL	0,138	0,141	0,237	0,098	0,161	0,178	0,204
OlPkTesL	0,147	0,148	0,246	0,104	0,172	0,187	0,207
OspPkTesL	0,153	0,151	0,247	0,104	0,172	0,19	0,202
ScPkTesL	0,126	0,126	0,199	0,092	0,143	0,156	0,183
AqPkTesL	0,13	0,13	0,198	0,093	0,138	0,159	0,167
EmPkTesL	0,133	0,13	0,212	0,09	0,139	0,163	0,171
AvPkTesL	0,128	0,127	0,21	0,092	0,148	0,16	0,193
OmPkTesL	0,129	0,127	0,209	0,1	0,15	0,16	0,189
MlPkTesL	0,142	0,14	0,196	0,092	0,151	0,156	0,162
SrPkTesL	0,083	0,079	0,124	0,064	0,092	0,097	0,109

Seq->	MmTes	DmTes	ChTes	OcPkTesL	OlPkTesL	OspPkTesL	ScPkTesL
MmPkL1	0,117	0,078	0,136	0,138	0,147	0,153	0,126
MmPkL2	0,115	0,075	0,129	0,141	0,148	0,151	0,126
MmPkL3	0,188	0,118	0,196	0,237	0,246	0,247	0,199
DmPk	0,081	0,06	0,086	0,098	0,104	0,104	0,092
DmEsn	0,13	0,082	0,139	0,161	0,172	0,172	0,143
ChPk	0,144	0,099	0,152	0,178	0,187	0,19	0,156
TaPk	0,169	0,103	0,185	0,204	0,207	0,202	0,183
MmTes	ID	0,173	0,345	0,337	0,329	0,335	0,25
DmTes	0,173	ID	0,167	0,165	0,171	0,169	0,142
ChTes	0,345	0,167	ID	0,38	0,396	0,41	0,301
OcPkTesL	0,337	0,165	0,38	ID	0,763	0,787	0,392
OlPkTesL	0,329	0,171	0,396	0,763	ID	0,835	0,377
OspPkTesL	0,335	0,169	0,41	0,787	0,835	ID	0,38
ScPkTesL	0,25	0,142	0,301	0,392	0,377	0,38	ID
AqPkTesL	0,282	0,134	0,301	0,382	0,391	0,387	0,322
EmPkTesL	0,289	0,146	0,344	0,427	0,428	0,438	0,332
AvPkTesL	0,255	0,141	0,314	0,399	0,419	0,424	0,307
OmPkTesL	0,244	0,149	0,319	0,406	0,419	0,413	0,302
MlPkTesL	0,243	0,109	0,247	0,3	0,297	0,304	0,257
SrPkTesL	0,15	0,111	0,154	0,19	0,182	0,183	0,205

Seq->	AqPkTesL	EmPkTesL	AvPkTesL	OmPkTesL	MlPkTesL	SrPkTesL
MmPkL1	0,13	0,133	0,128	0,129	0,142	0,083
MmPkL2	0,13	0,13	0,127	0,127	0,14	0,079
MmPkL3	0,198	0,212	0,21	0,209	0,196	0,124
DmPk	0,093	0,09	0,092	0,1	0,092	0,064
DmEsn	0,138	0,139	0,148	0,15	0,151	0,092
ChPk	0,159	0,163	0,16	0,16	0,156	0,097
TaPk	0,167	0,171	0,193	0,189	0,162	0,109
MmTes	0,282	0,289	0,255	0,244	0,243	0,15
DmTes	0,134	0,146	0,141	0,149	0,109	0,111
ChTes	0,301	0,344	0,314	0,319	0,247	0,154
OcPkTesL	0,382	0,427	0,399	0,406	0,3	0,19
OlPkTesL	0,391	0,428	0,419	0,419	0,297	0,182
OspPkTesL	0,387	0,438	0,424	0,413	0,304	0,183
ScPkTesL	0,322	0,332	0,307	0,302	0,257	0,205
AqPkTesL	ID	0,465	0,327	0,337	0,243	0,165
EmPkTesL	0,465	ID	0,376	0,377	0,277	0,175
AvPkTesL	0,327	0,376	ID	0,665	0,251	0,173
OmPkTesL	0,337	0,377	0,665	ID	0,254	0,171
MlPkTesL	0,243	0,277	0,251	0,254	ID	0,142
SrPkTesL	0,165	0,175	0,173	0,171	0,142	ID

Abbreviations. Vertebrate: Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Cnidaria: Ch, *Clytia hemisphaerica.* Placozoa: Ta, *Trichoplax adhaerens*. Porifera: Aq, *Amphimedon queenslandica*; Av, *Aphrocalistes vastus*; Em, *Ephydatia muelleri*; *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; *Om, Oopsacas minuta*; *Osp, Oscarella sp*.; Sc, *Sycon ciliatum*. Ctenophora: Ml, *Mnemiopsis leidyi*. Choanoflagellata: Sr, *Salpingoeca rosetta*.

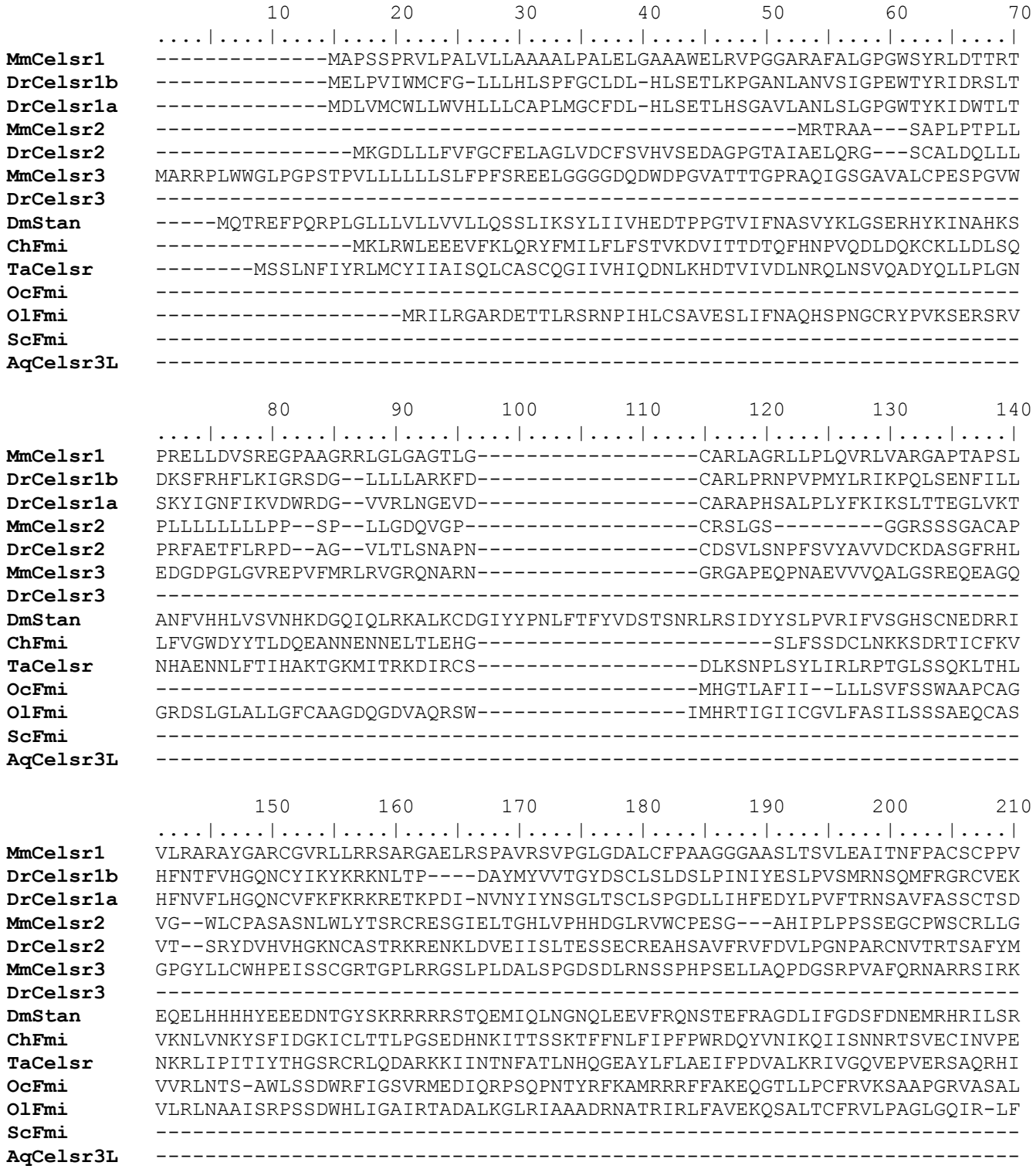
Table S2.6: Strabismus/Van Gogh/Stan sequence identity matrix. Obtained using bioedit software.

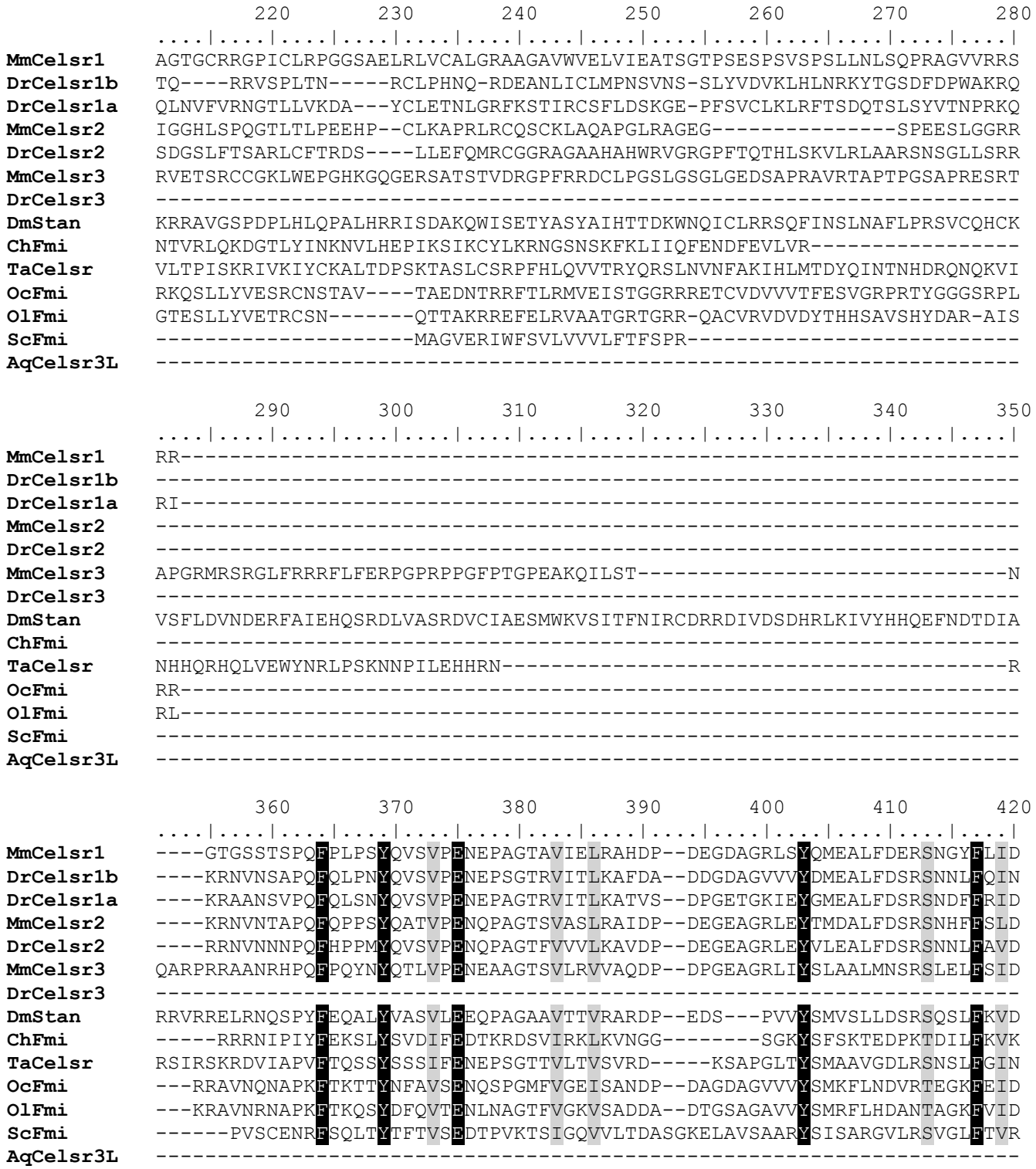
Seq->	MmVangL1	DrVangL1	MmVangL2	DrVangL2	DmVang	ChStbm	TaVang
MmVangL1	ID	0,648	0,708	0,644	0,422	0,366	0,321
DrVangL1	0,648	ID	0,628	0,608	0,397	0,365	0,305
MmVangL2	0,708	0,628	ID	0,768	0,414	0,373	0,309
DrVangL2	0,644	0,608	0,768	ID	0,413	0,363	0,31
DmVang	0,422	0,397	0,414	0,413	ID	0,287	0,267
ChStbm	0,366	0,365	0,373	0,363	0,287	ID	0,332
TaVang	0,321	0,305	0,309	0,31	0,267	0,332	ID
OcVang	0,272	0,271	0,252	0,259	0,251	0,277	0,294
OlVang	0,27	0,276	0,253	0,255	0,245	0,274	0,286
OspVang	0,244	0,251	0,23	0,228	0,219	0,238	0,212

Seq->	OcVang	OlVang	OspVang
MmVangL1	0,272	0,27	0,244
DrVangL1	0,271	0,276	0,251
MmVangL2	0,252	0,253	0,23
DrVangL2	0,259	0,255	0,228
DmVang	0,251	0,245	0,219
ChStbm	0,277	0,274	0,238
TaVang	0,294	0,286	0,212
OcVang	ID	0,75	0,564
OlVang	0,75	ID	0,605
OspVang	0,564	0,605	ID

Abbreviations. Vertebrate: Dr, *Danio rerio* and Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Cnidaria: Ch, *Clytia hemisphaerica.* Placozoa: Ta, *Trichoplax adhaerens*. Porifera: *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; *Om, Oopsacas minuta*; *Osp, Oscarella sp*.

Figure S2.1: Flamingo/Celsr/Stan alignment. Threshold for shading has been fixed at 80% for both identity (black) and similarity (grey).

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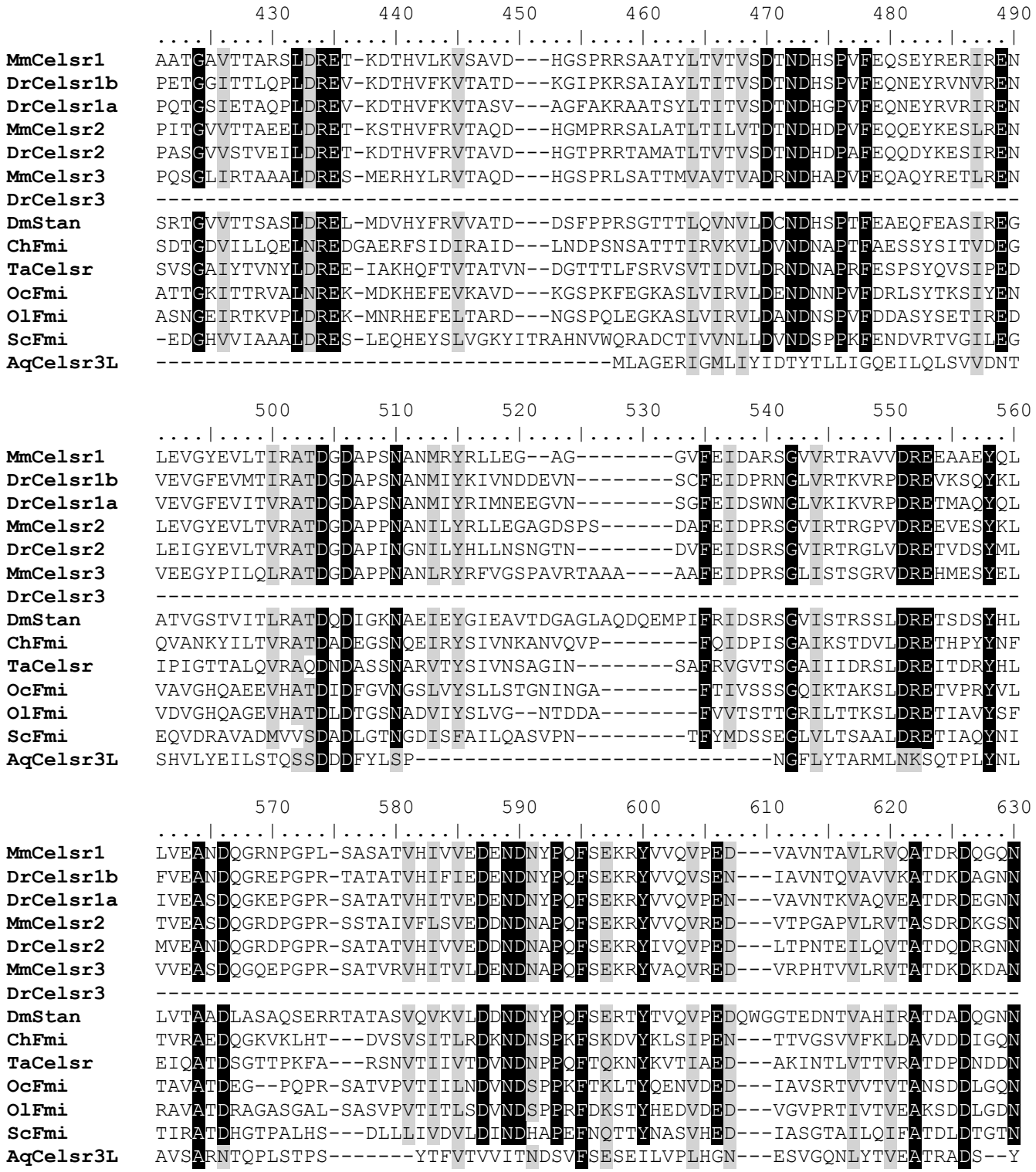
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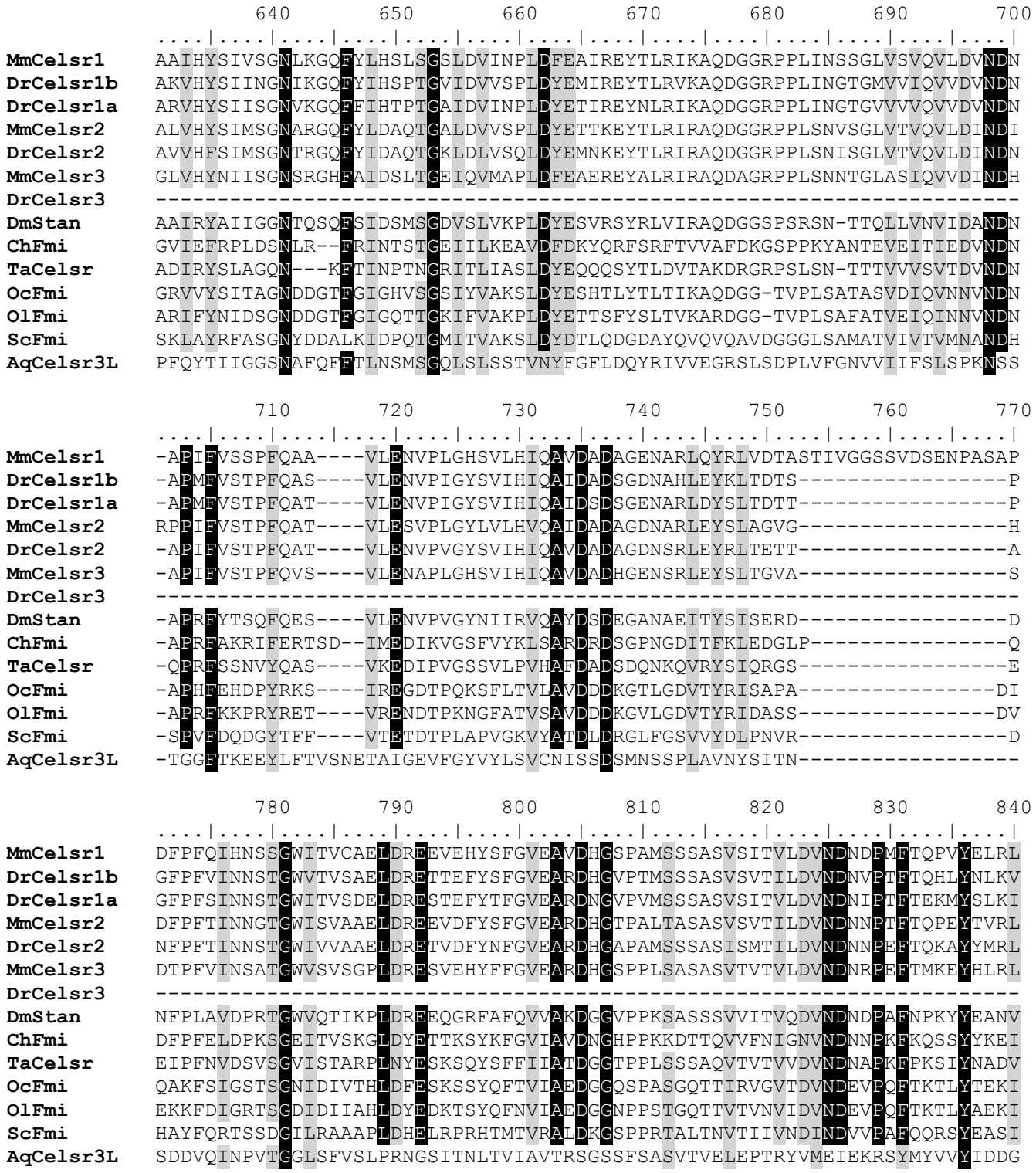
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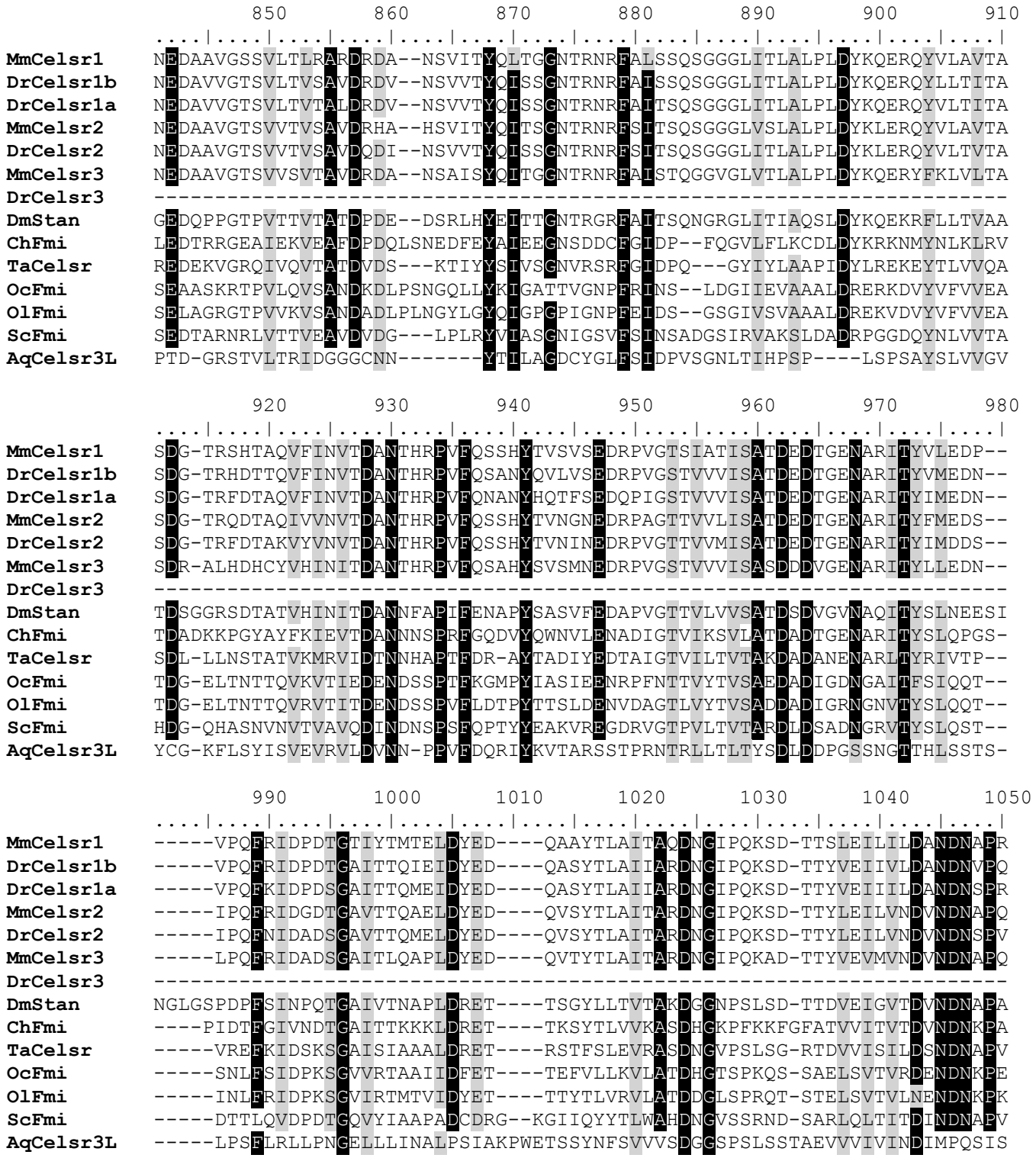
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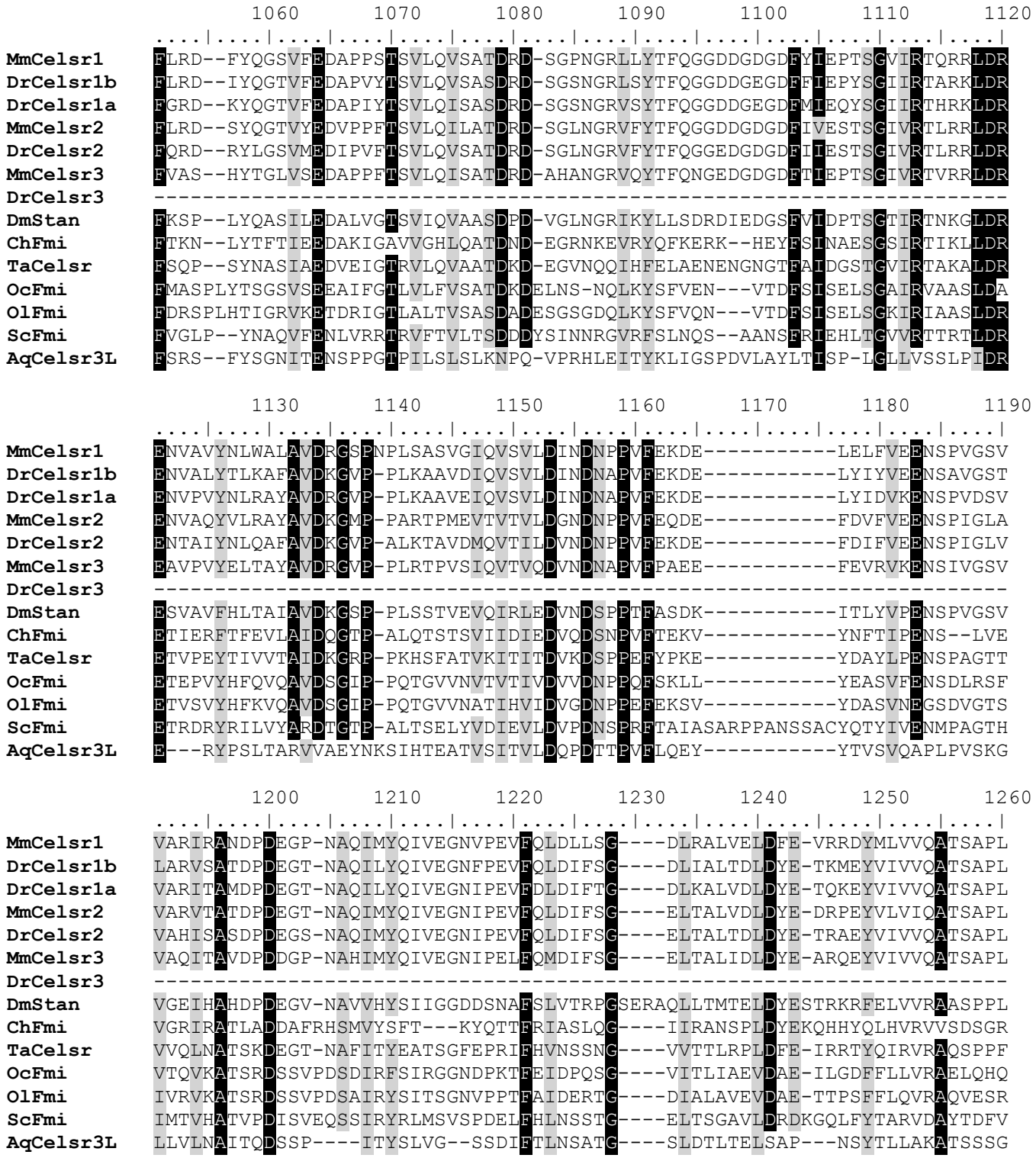
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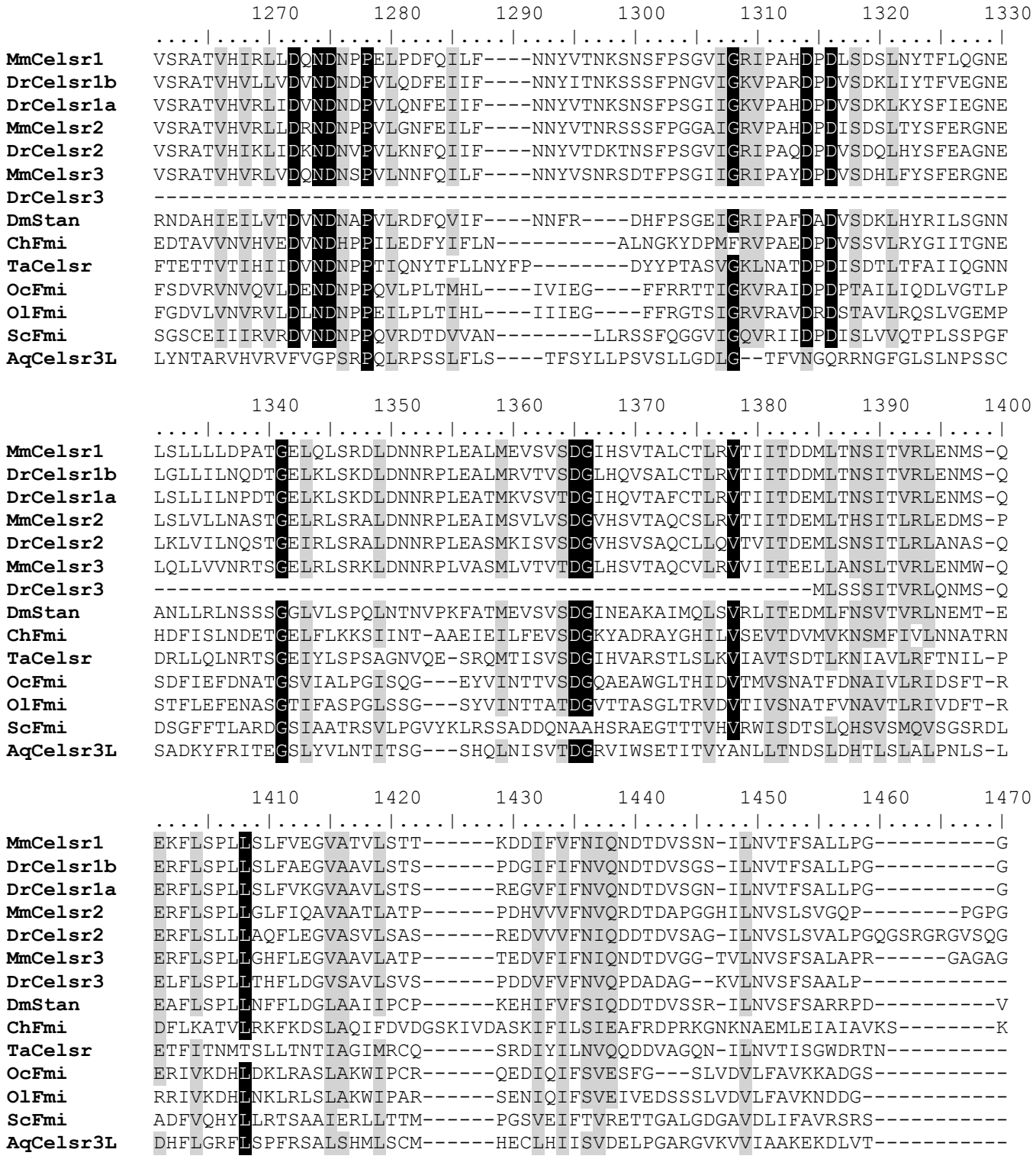
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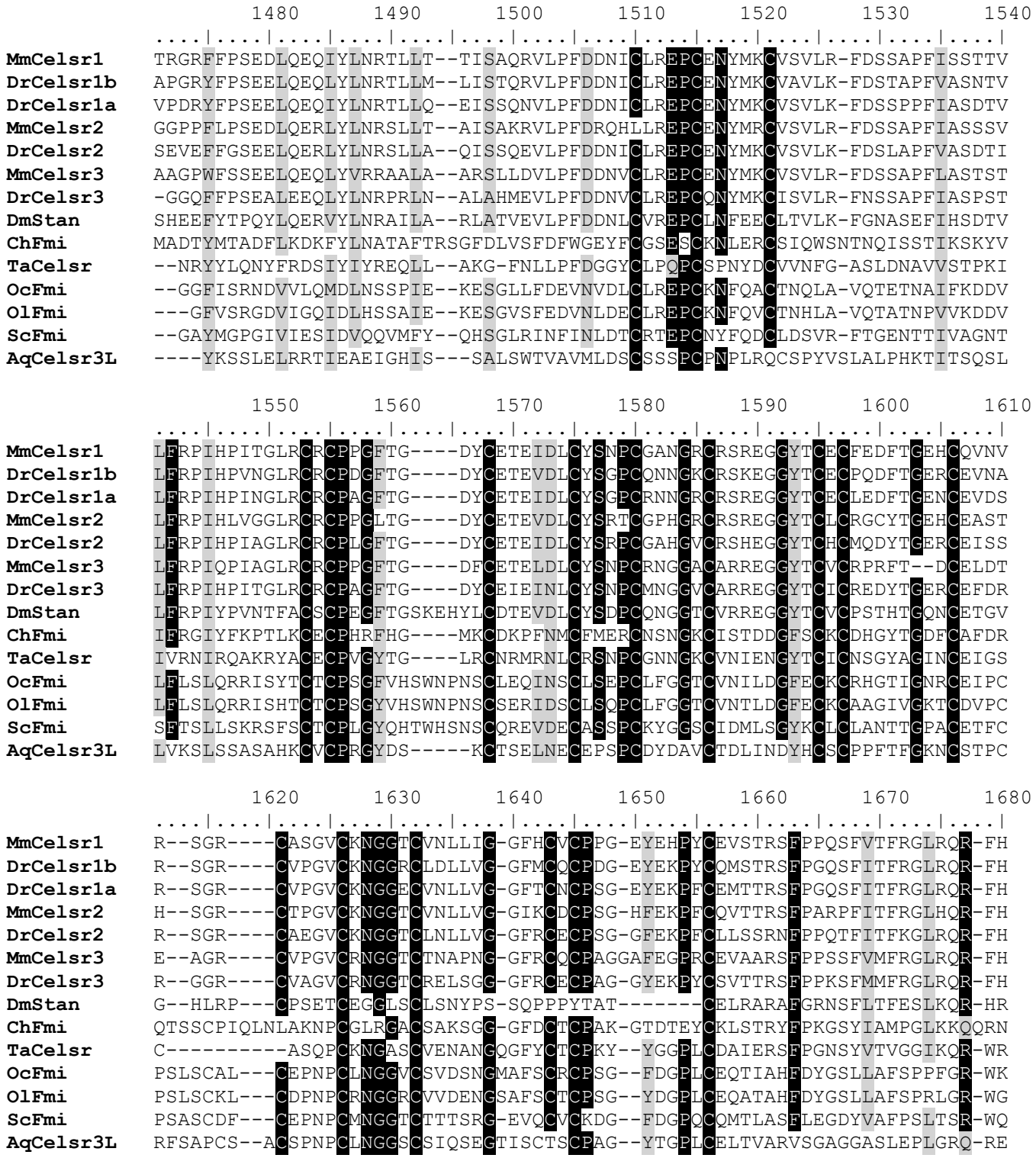
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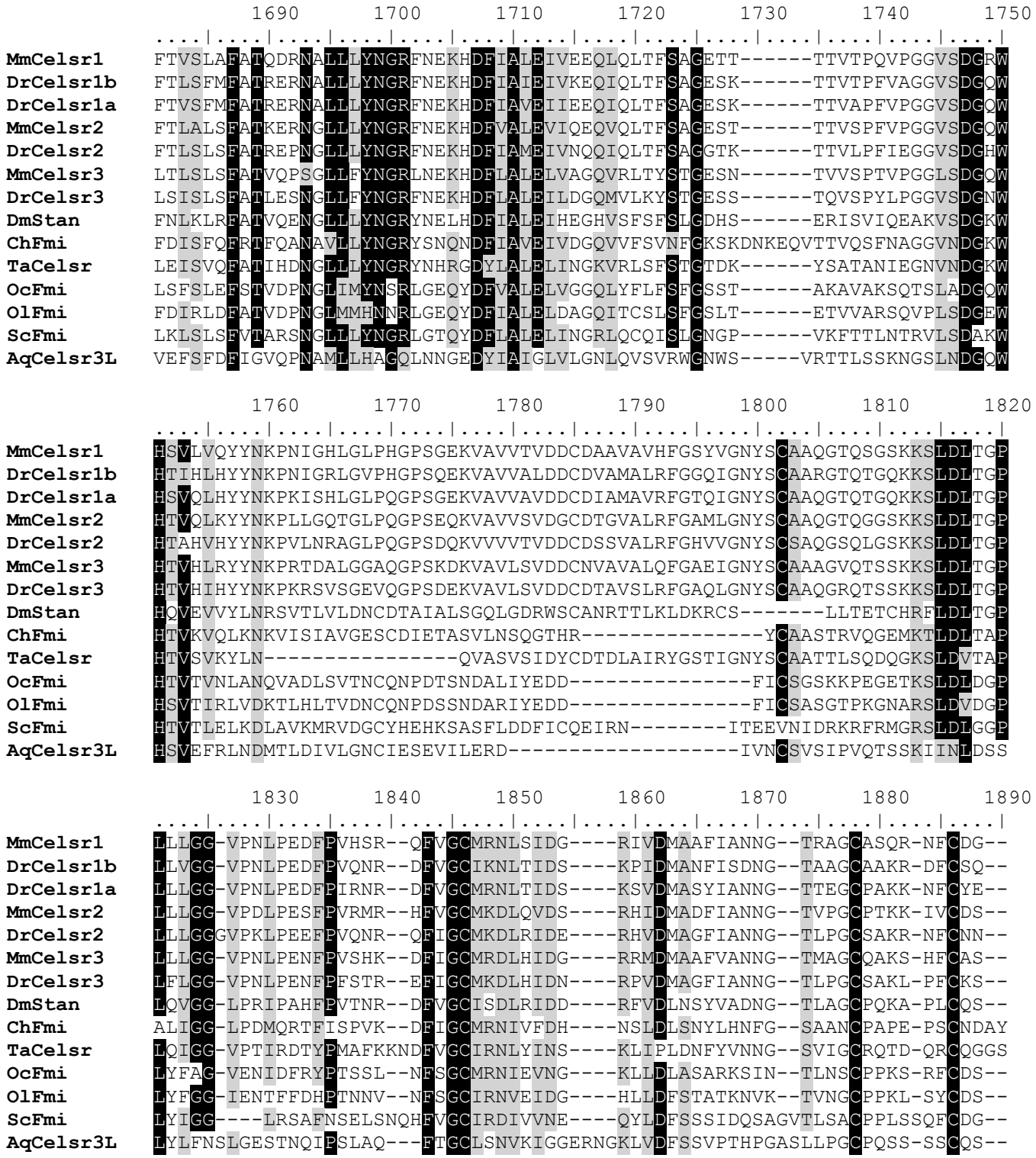
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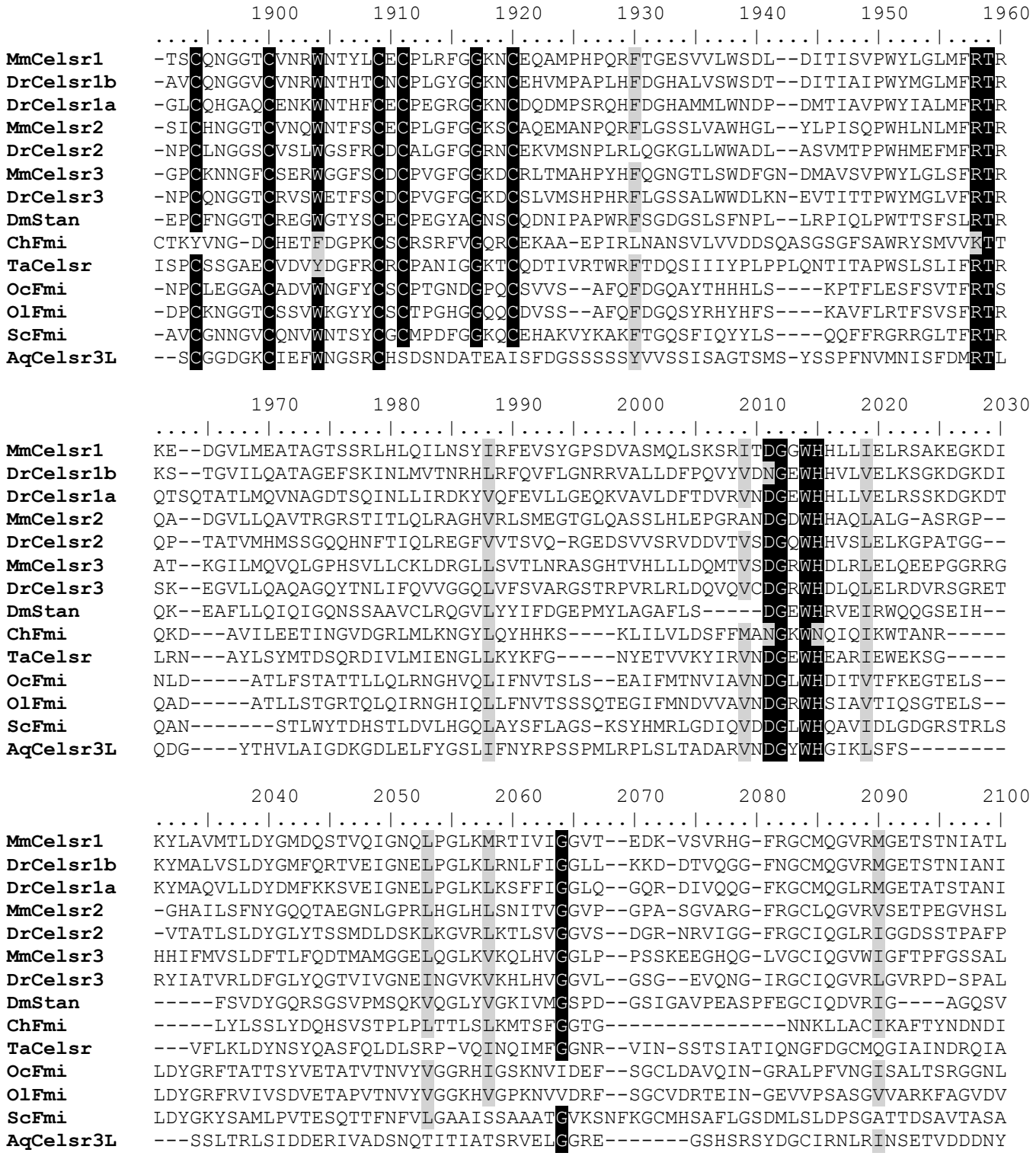
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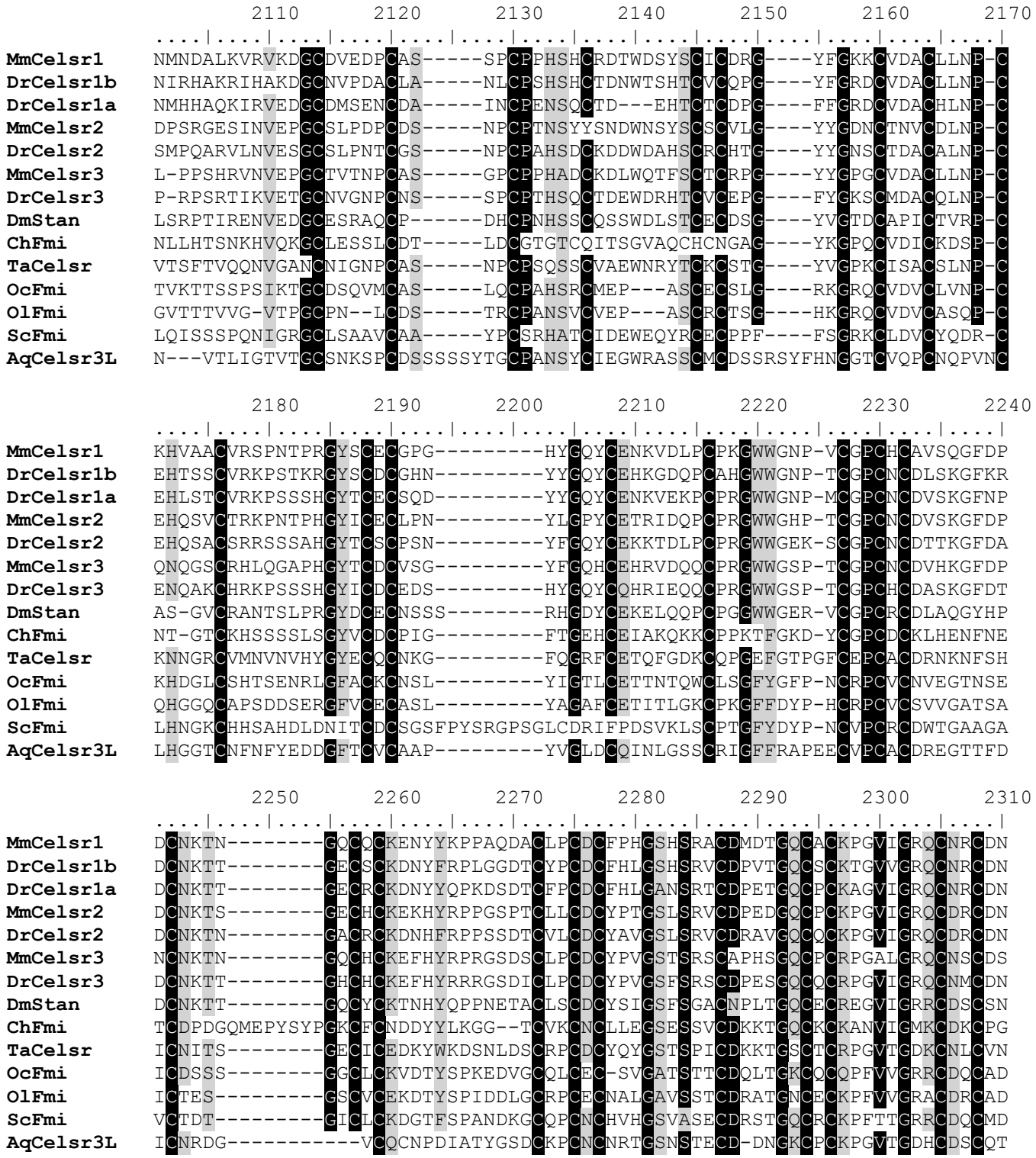
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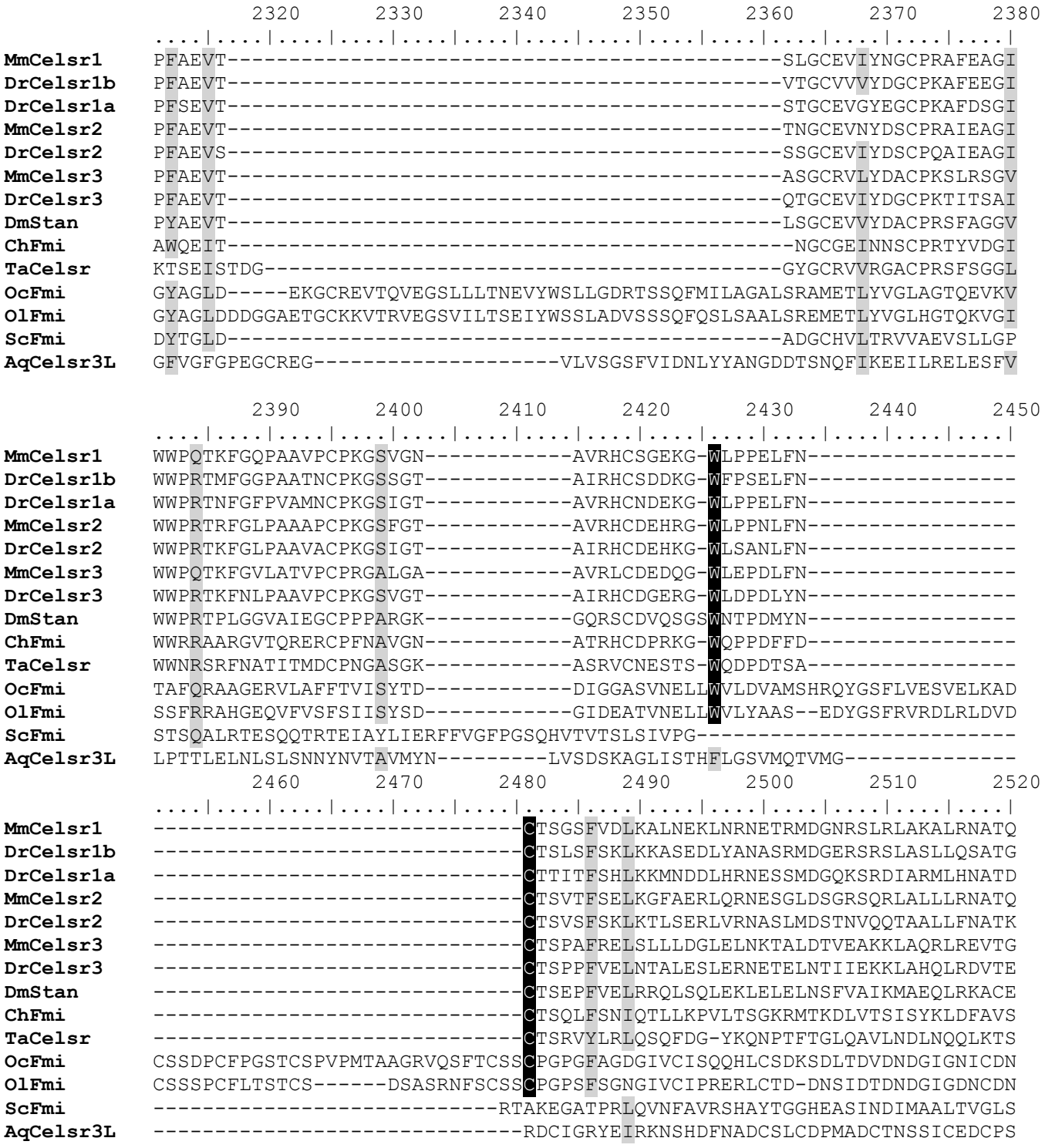
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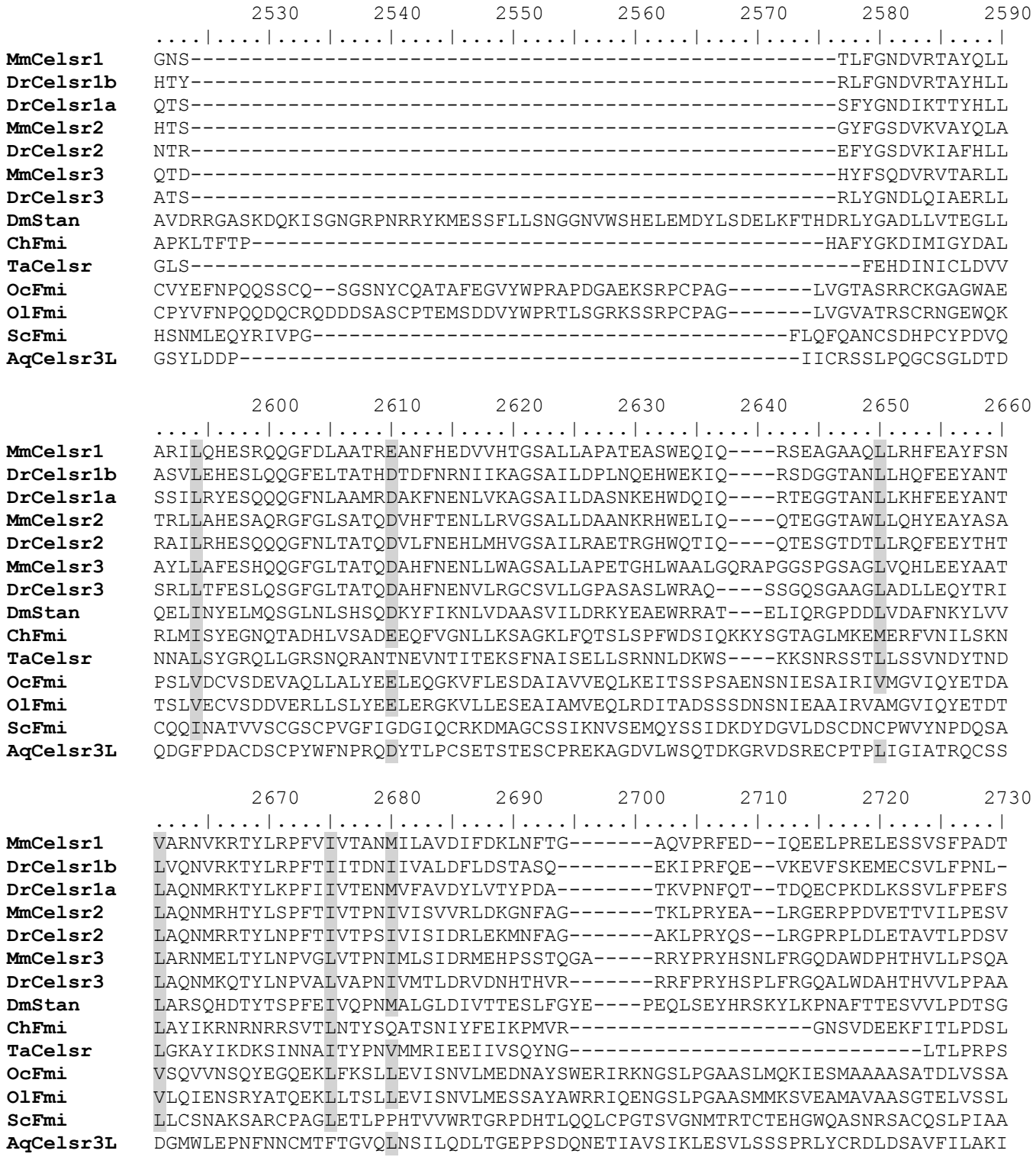
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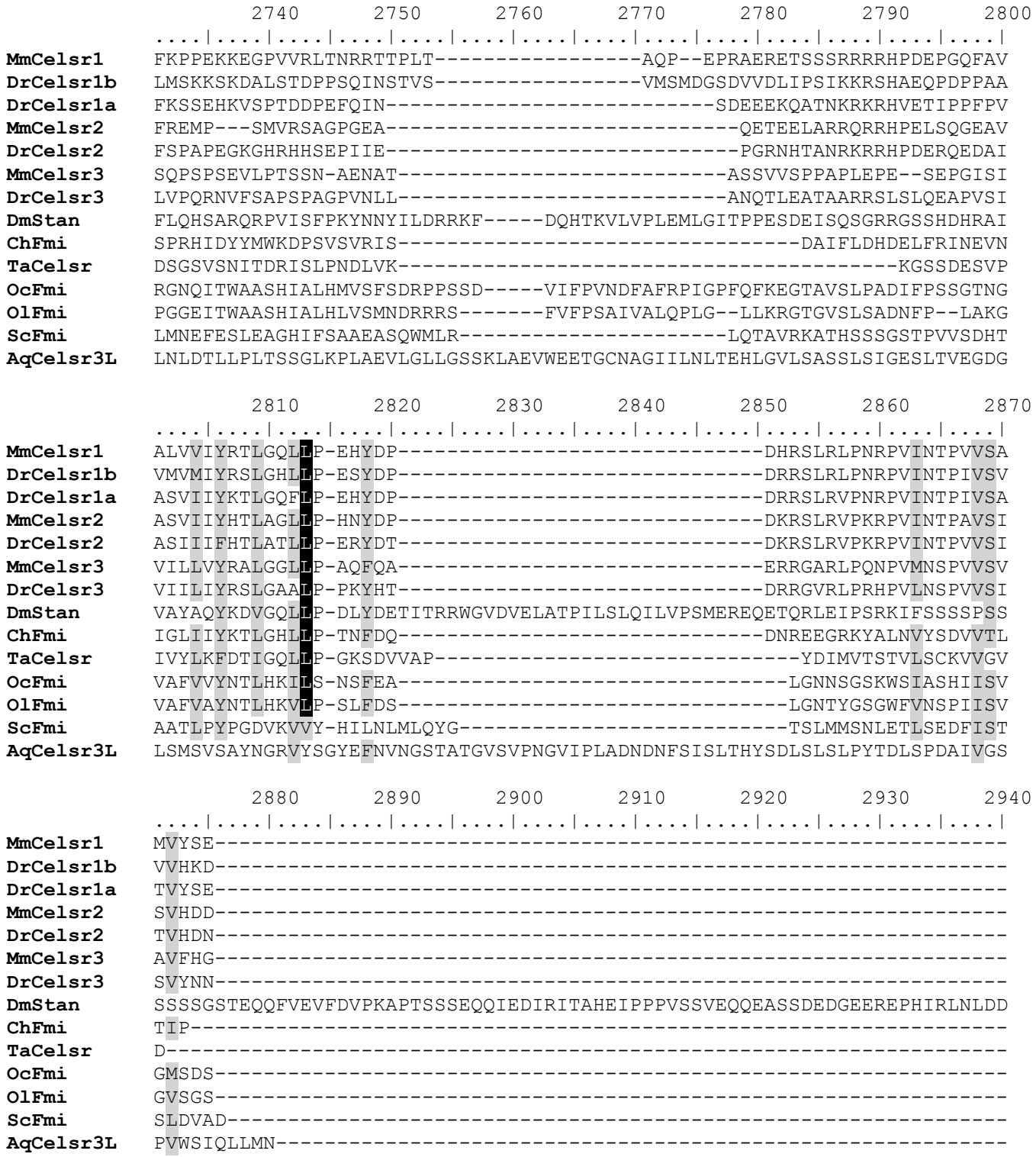
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DrCelsr3 SVYNN----------
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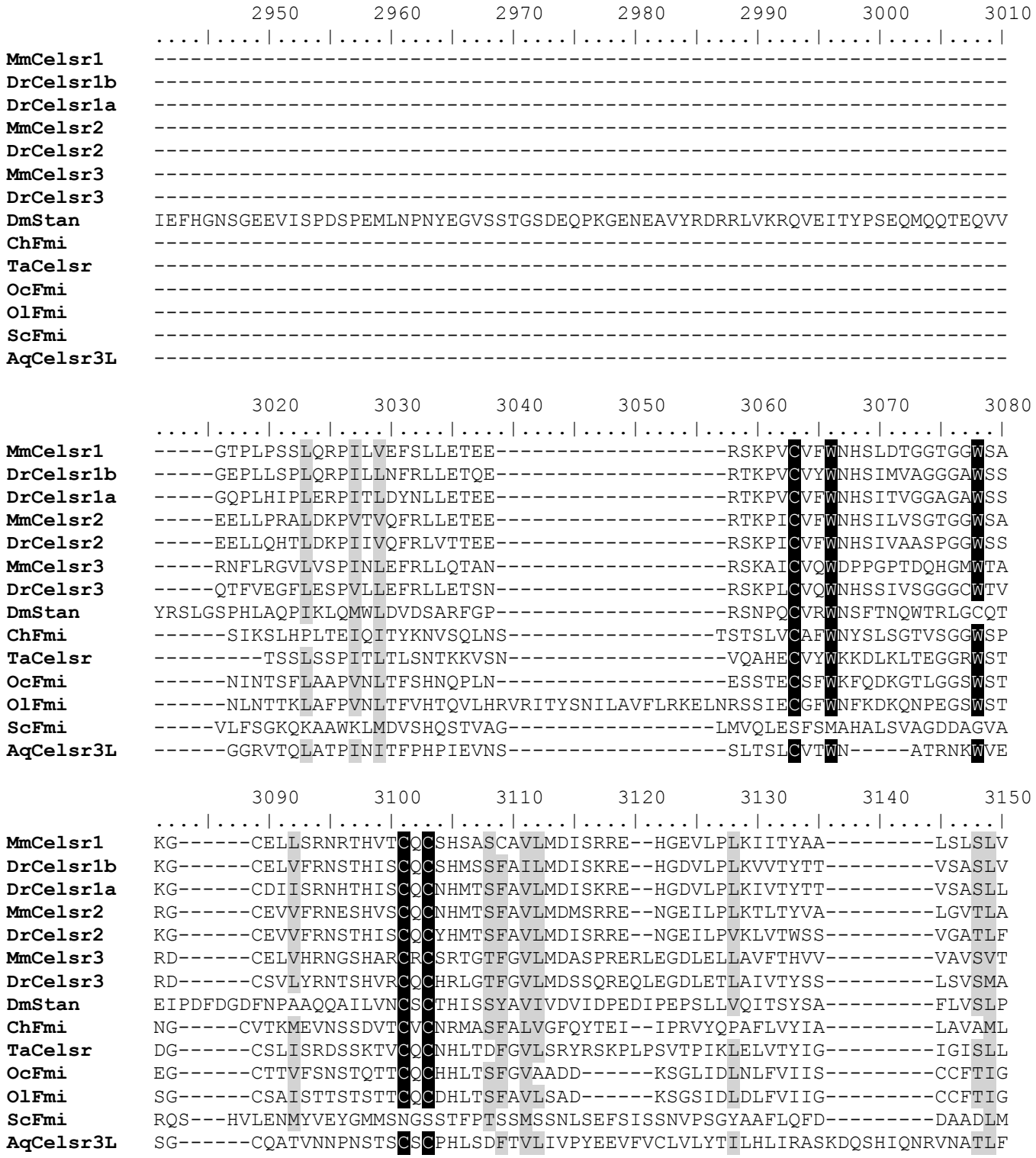
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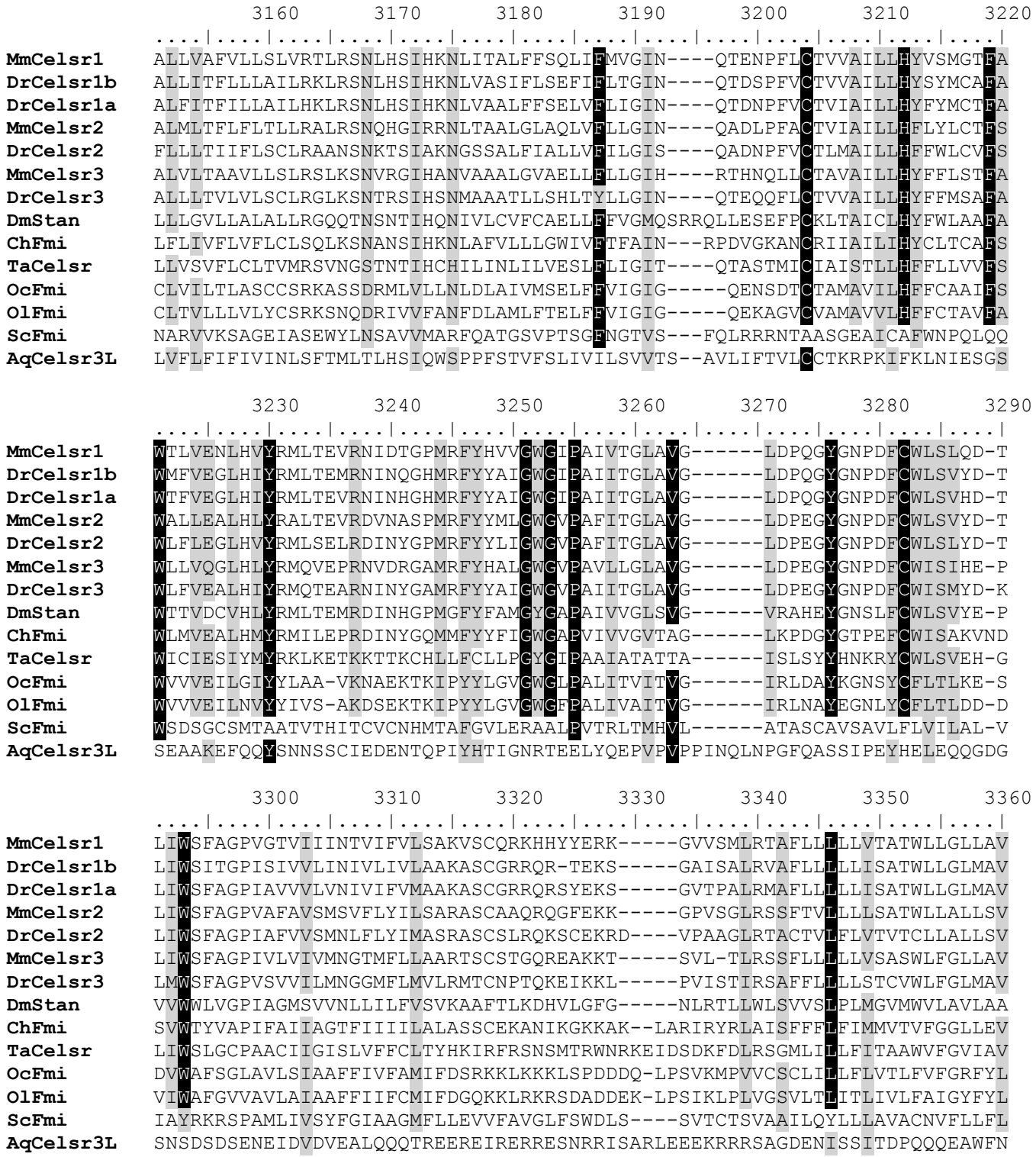
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OlFmi CLTVLLLVLYCSRKSNQDRIVVFANFDLAMLFTELFFVIGIG-----QEKAGVCVAMAVVLHFFCTAVFA
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ScFmi WSDSGCSMTAATVTHITCVCNHMTAFGVLERAALPVTRLTMHVL------ATASCAVSAVLFLVILAL-V
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ScFmi IAYRKRSPAMLIVSYFGIAAGMFLLEVVFAVGLFSWDLS----SVTCTSVAAILQYLLLAVACNVFLLFL
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DrCelsr1a  NSDVMTFHYLFAIFSCLQGVFIFFFHIVFNKEVRKNLKNVFTGKKQLPDESSTTRTTLLTRTLNCNNTYM
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TaCelsr    QNETVYFQYIFTMVNFIKSACILICYCISNESVRSELSARLCGREGTYYTGTIDKGQLNGHRSNGLNGHF
OcFmi      INSTSAWSYGFGIINLLLGLVLFITQLLQISKLRKWYMGESSKSRGQYHVSSAQPTRSILSGSFGGDKTN
OlFmi      PRSSSSLKYAFGTFNILLGFVFLACQILQVSKEVRYIR----------HMSVFL-------------IVD
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OcFmi      LSVSFTGTYKSHPYTGNPMFSSGPQWDRNVP-----------------DQSYDAMEMDREEDWDEEGIAF
OlFmi      LAYKSHGTVQAYP-VANPMY--GHHWDHGE-------------------QSYDEIDNDREEDWDED--AL
ScFmi      FYVPPAALCTVTFILAMGLAGASRNATHQAR-------------------WNTVWMIVFCLGFGCAFLLL
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OlFmi      ---FDN-DKPPLEDVAEEPEEFDLEEIHERSNRGRARYPLSAVDSPARTKGTYLQSPVHKS-----SEEK
ScFmi      ---QSILNPPSALPAAAPLSEQHFVPMPHTTNSGSSHSRRSHSSHRTPPPVWYLVEGTSGG--ITASKHS
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DmStan     ISPNPLPNPDLTDTSYLQQHHNKINMPPSILENIRDAREGYEDSLYGRRGEYPDKYGSYKPPSHYGSEKD
ChFmi      SSNTDSDTQSQSKAPVSILKKKSQYDSKGHRLRAVRVKDSQRKPLMSMNETADLNDSQV----------
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OcFmi      TTVSP----MSSGIEG--VMVRRAVESSSRESSIPQQKINHWKSQGGDDDSSSLSSSSTDSLSFGKGRGQ
OlFmi      TTVSPMTVEMSPGIEAGVVVVRQAIETSSRESSIPHQKPLWSMPKRRDVNDDDDDDDS-----------
ScFmi      AHTTTGSAASSALAAAAEYVSPYSLPPPPARVPTPPRISDFPTNPQDKQRPKQQQPRRNSAP--------
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                3720      3730      3740      3750      3760      3770      3780
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DrCelsr1b  ----------------------------------------------------------------------
DrCelsr1a  ----------------------------------------------------------------------
MmCelsr2   ----------------------------------------------------------------------
DrCelsr2   ----------------------------------------------------------------------
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DmStan     YPGGGSGSQTIGHMRSFHPDAAYLSDNIYDKQRTLGSGYLGAKSESPYLSKDRITPDIYGSRDGHYSLKR
ChFmi      ----------------------------------------------------------------------
TaCelsr    PGGPRHLVPKPPMRKGHPQPPPRSNPVKP----------------------------------------
OcFmi      VKGKGRHGKAQQRRRHLAGVEAGQHFSSASSLHSDFNSSVTSSQRNHRRG--------------------
OlFmi      ----------------------------------------------------------------------
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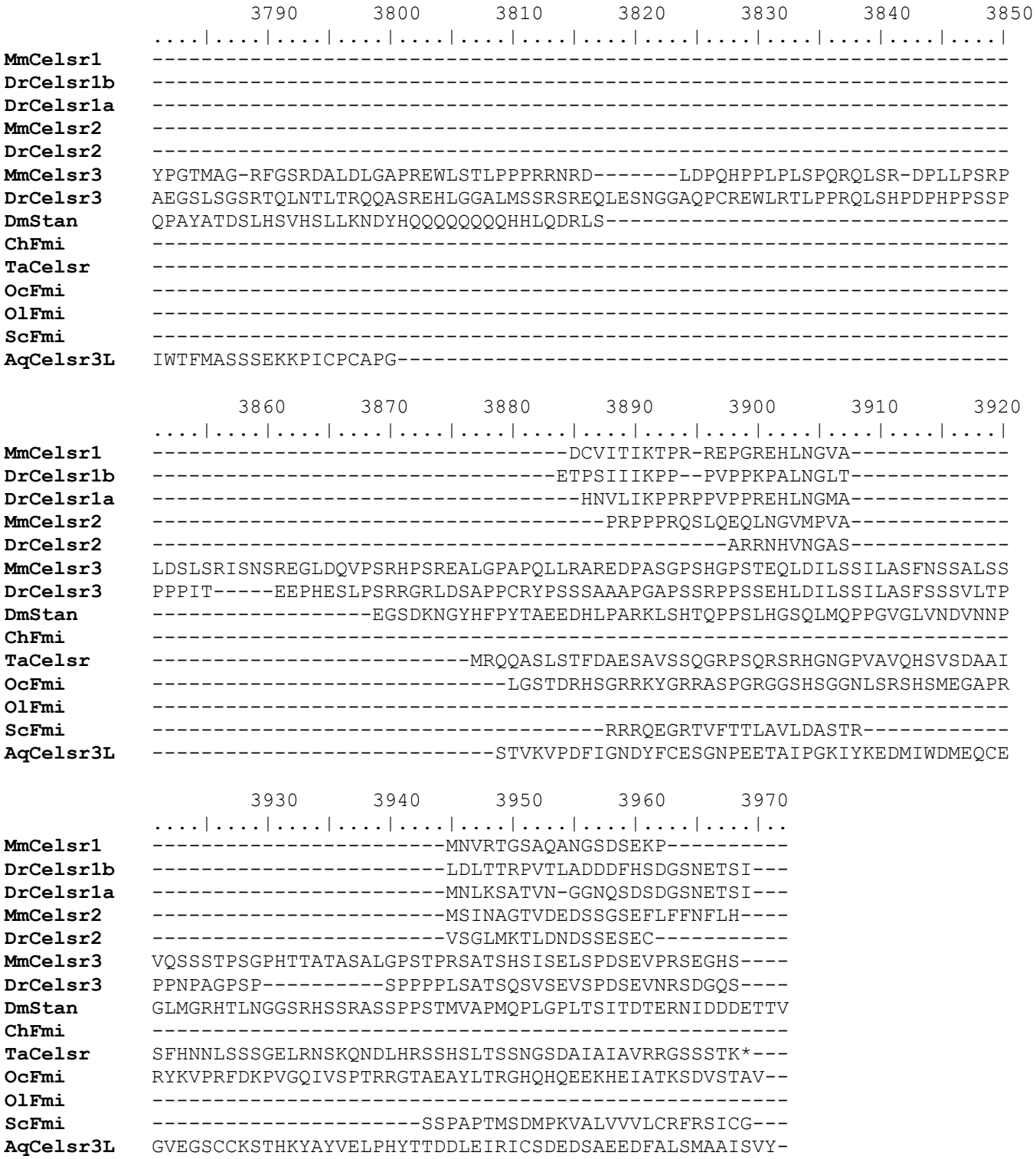
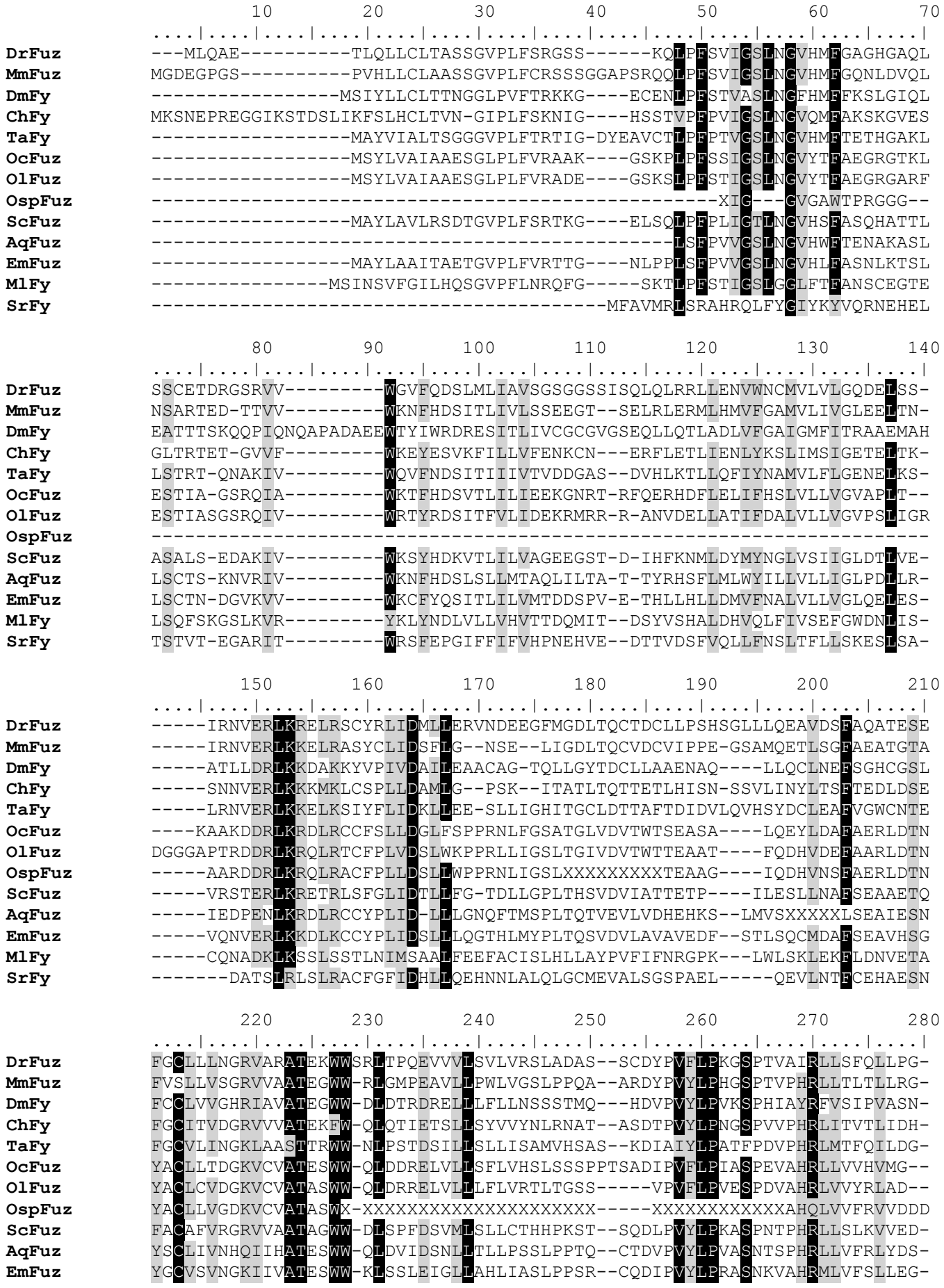
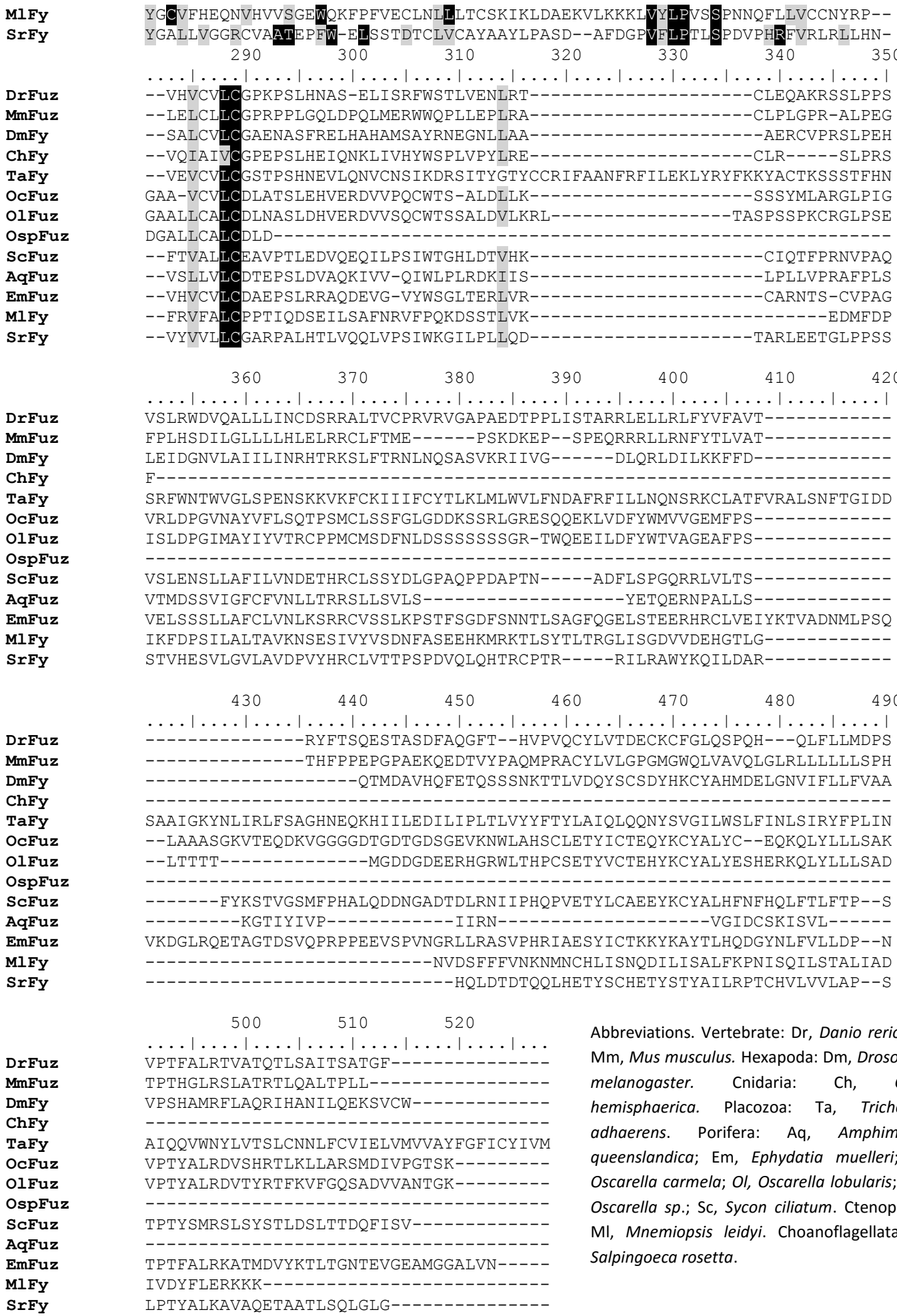


Abbreviations. Vertebrate: Dr, *Danio rerio* and Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Cnidaria: Ch, *Clytia hemisphaerica.* Placozoa: Ta, *Trichoplax adhaerens*. Porifera: Aq, *Amphimedon queenslandica*; *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; Sc, *Sycon ciliatum*.

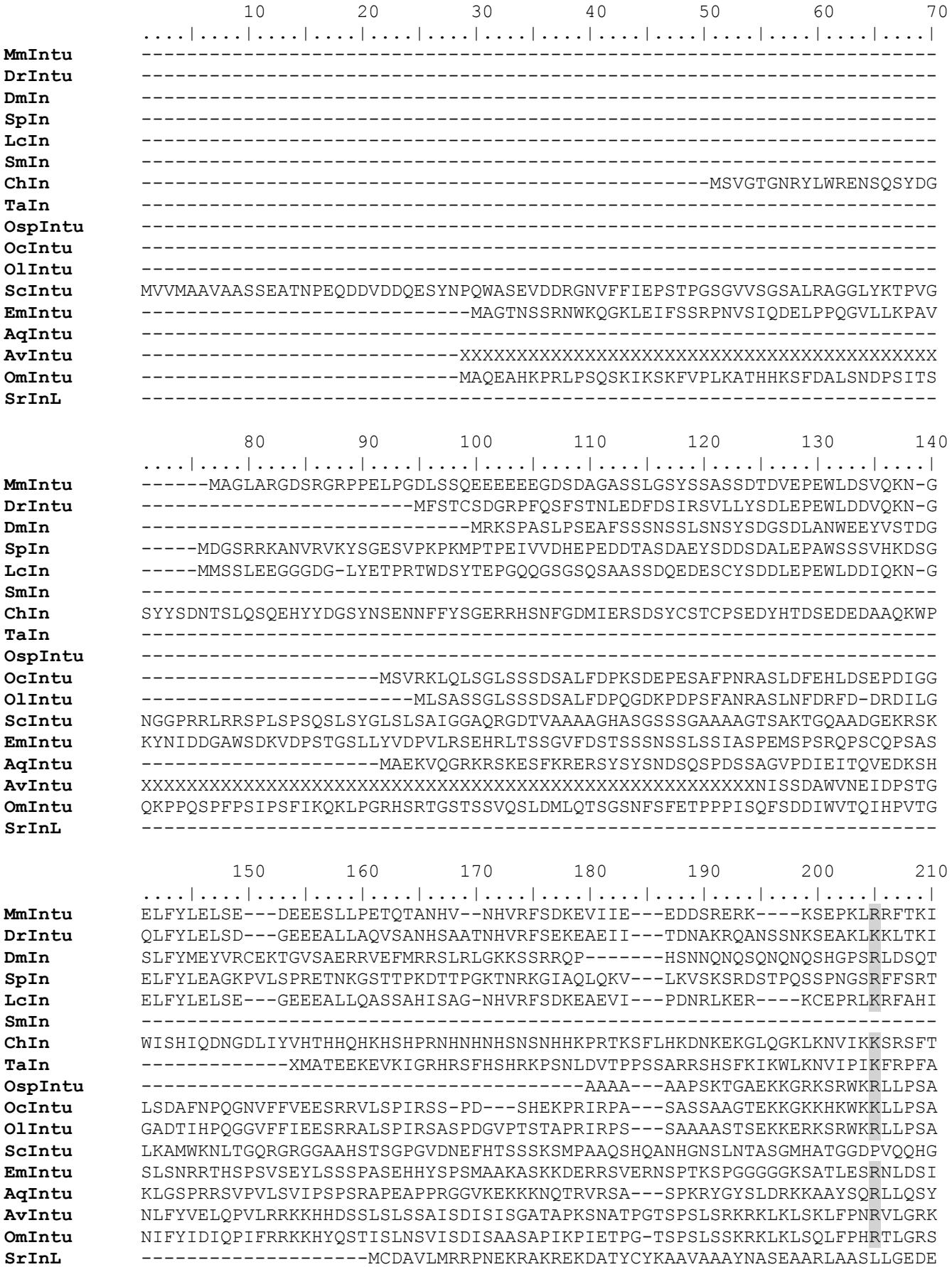
Figure S2.2: Fuzzy alignment. Threshold for shading has been fixed at 80% for both identity (black) and similarity (grey).

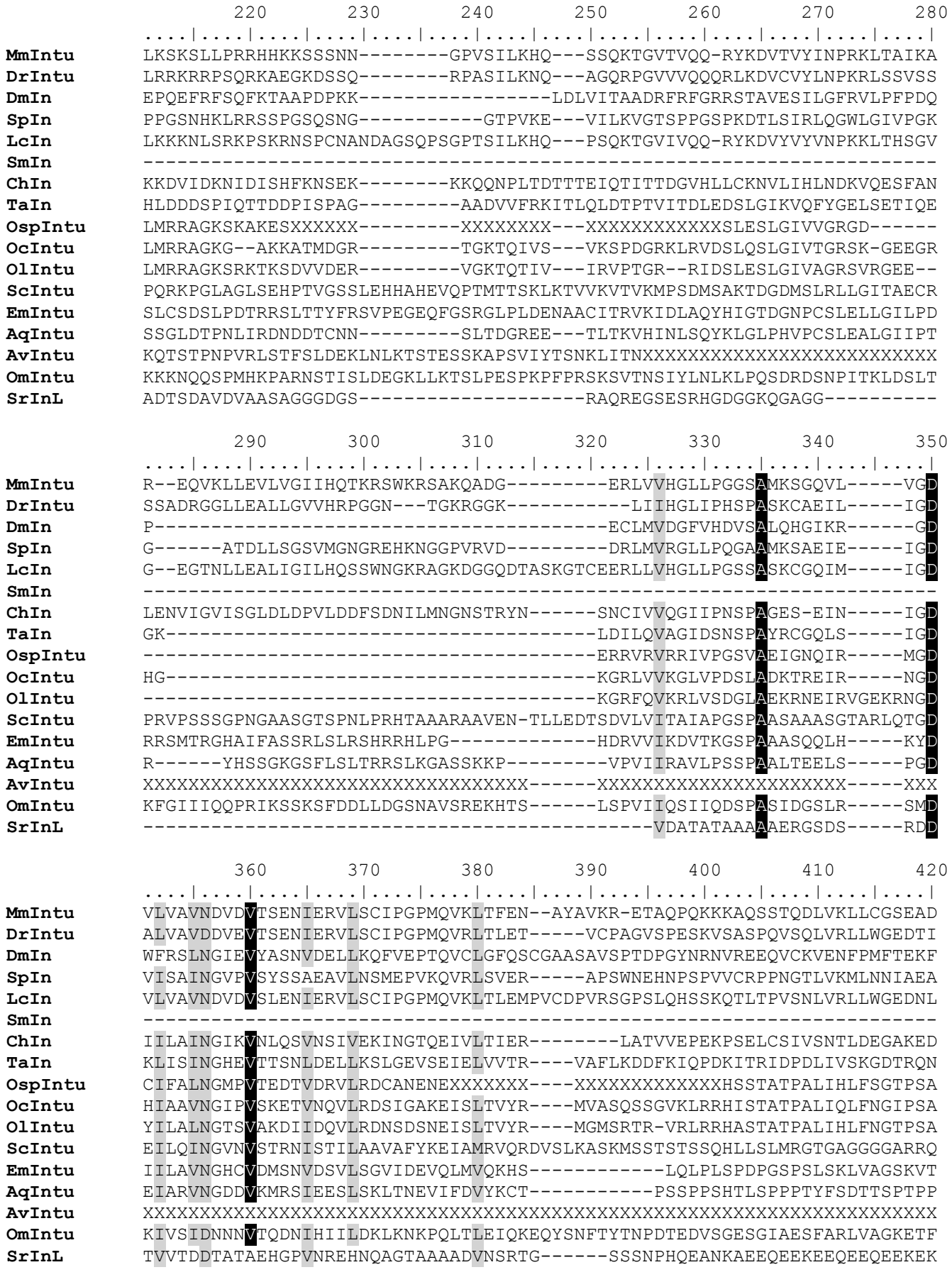




Abbreviations. Vertebrate: Dr, *Danio rerio* and Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Cnidaria: Ch, *Clytia hemisphaerica*. Placozoa: Ta, *Trichoplax adhaerens*. Porifera: Aq, *Amphimedon queenslandica*; Em, *Ephydatia muelleri*; *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; *Osp, Oscarella sp.*; Sc, *Sycon ciliatum*. Ctenophora: Ml, *Mnemiopsis leidyi*. Choanoflagellata: Sr, *Salpingoeca rosetta*.

Figure S2.3: Inturned alignment. Threshold for shading has been fixed at 80% for both identity (black) and similarity (grey). Red squares correspond to the three C-terminal motifs described in the present study.

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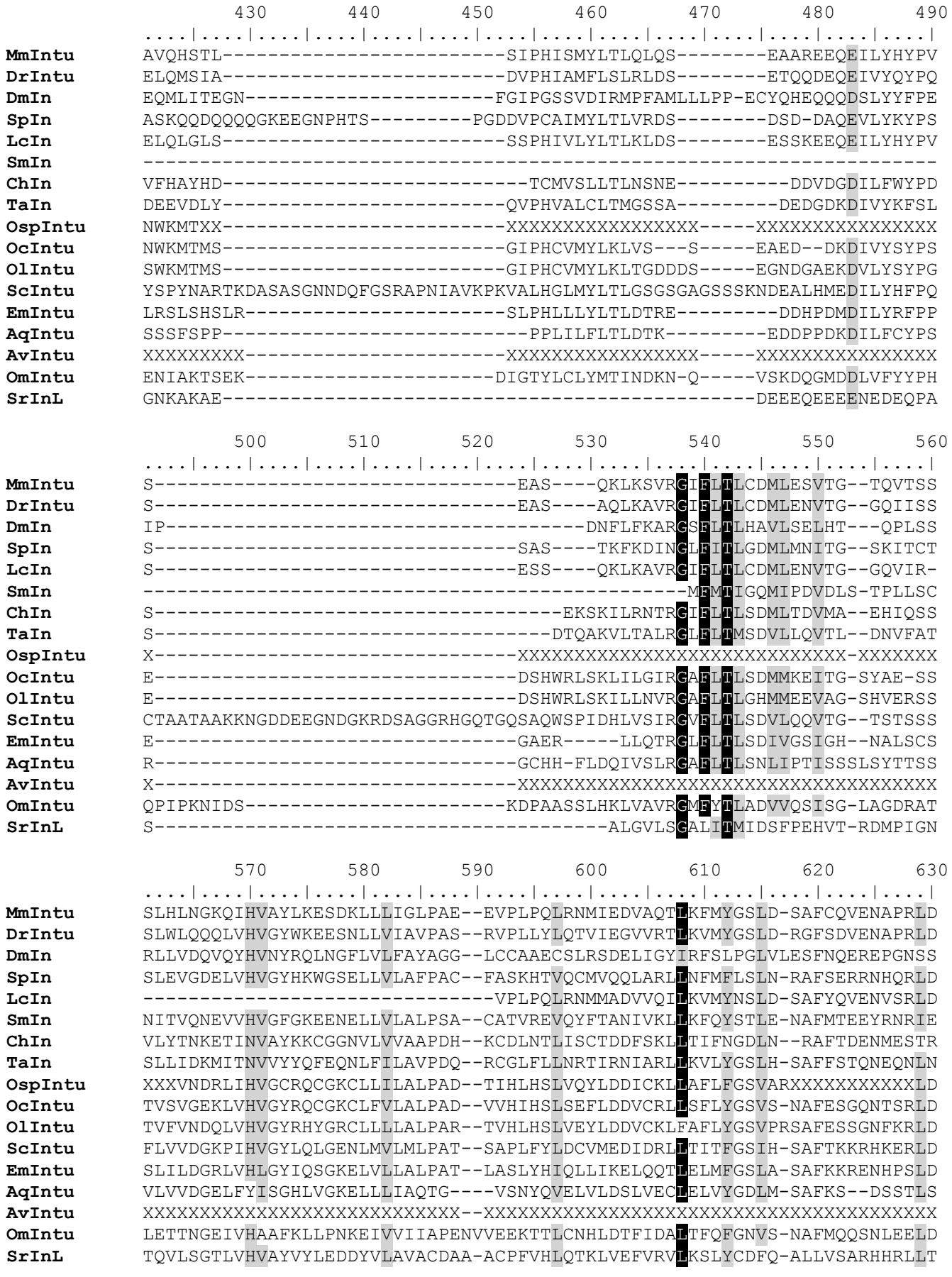
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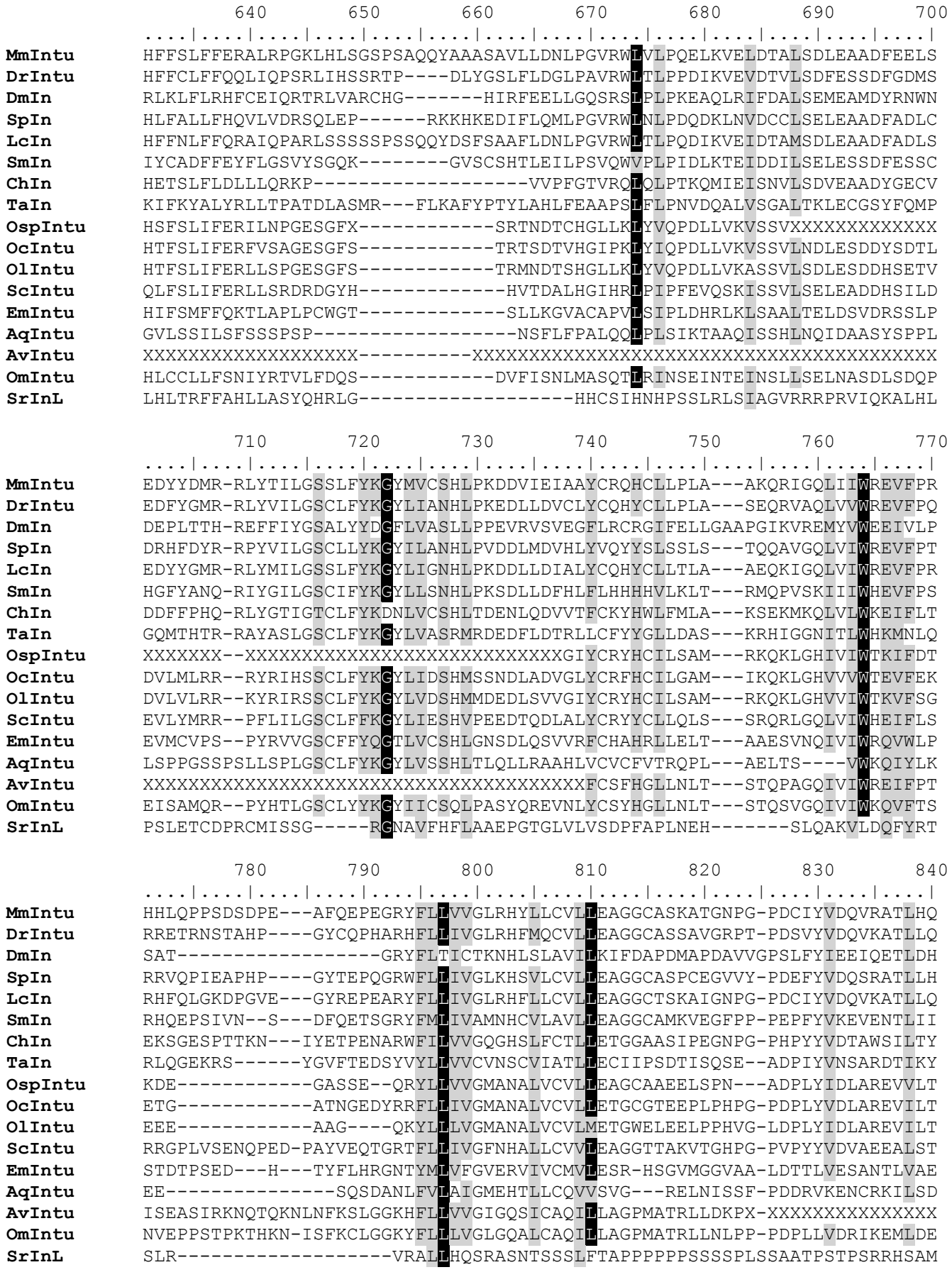
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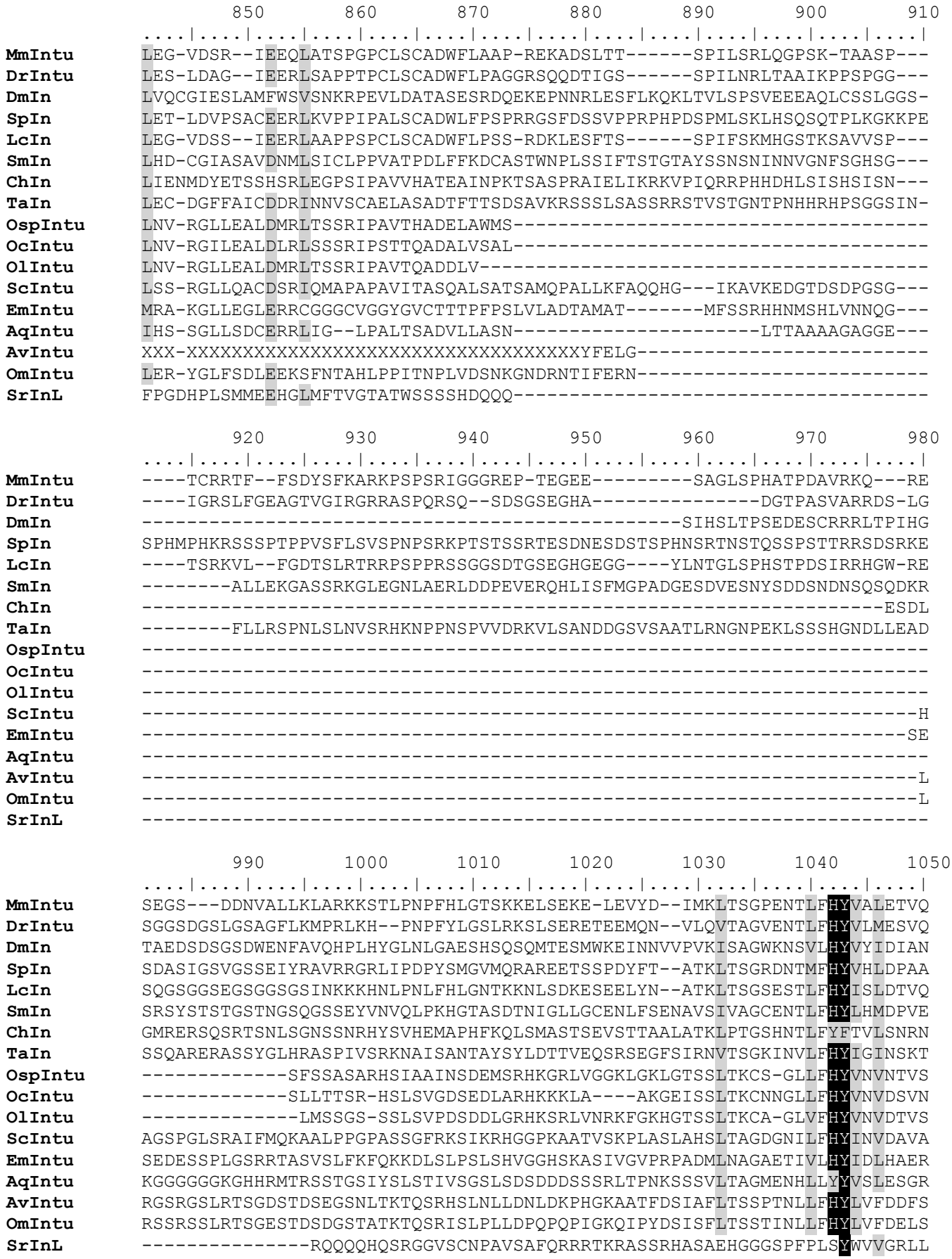
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ChIn GMRERSQSRTSNLSGNSSNRHYSVHEMAPHFKQLSMASTSEVSTTAALATKLPTGSHNTLFYFTVLSNRN
TaIn SSQARERASSYGLHRASPIVSRKNAISANTAYSYLDTTVEQSRSEGFSIRNVTSGKINVLFHYIGINSKT
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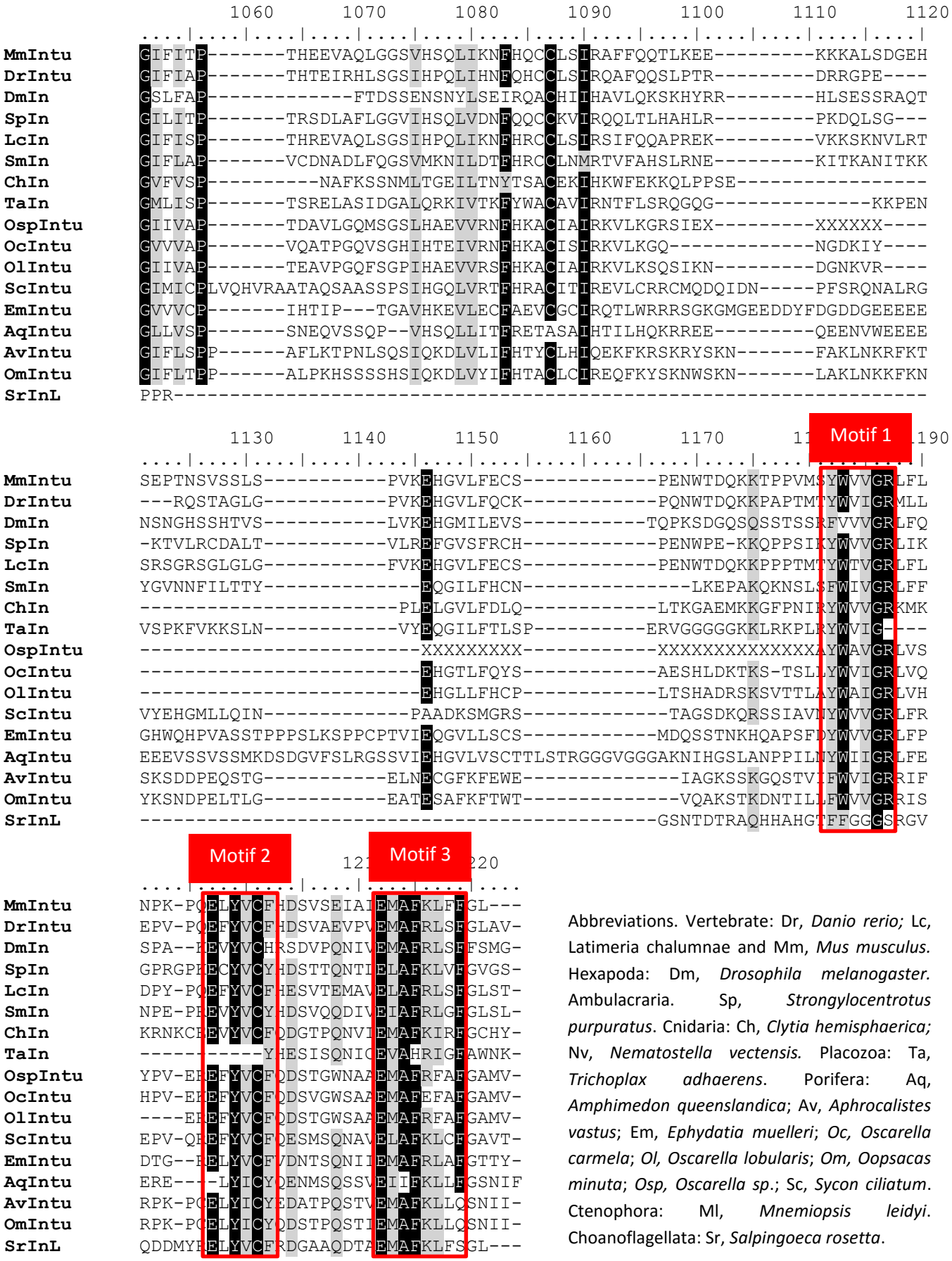
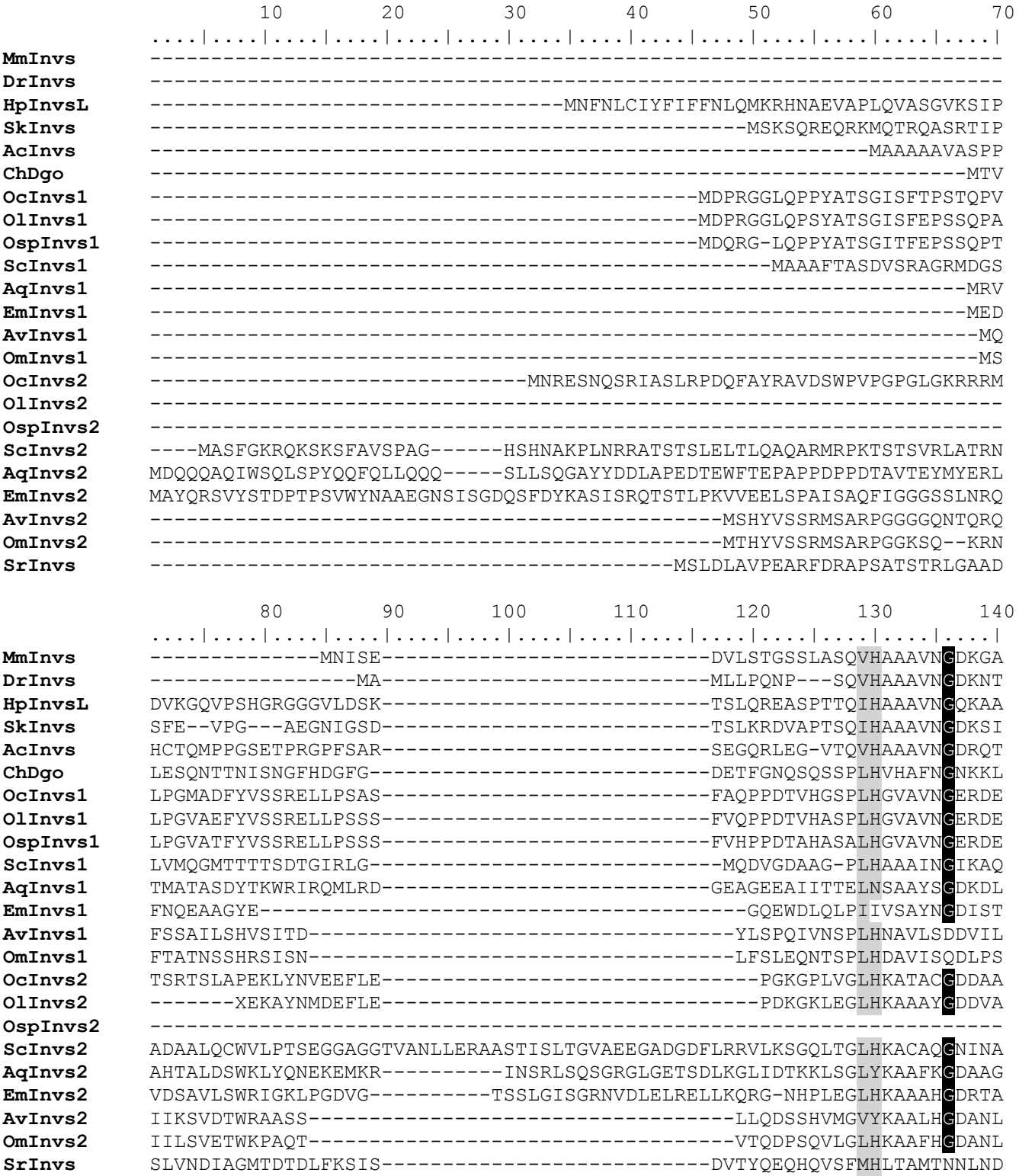
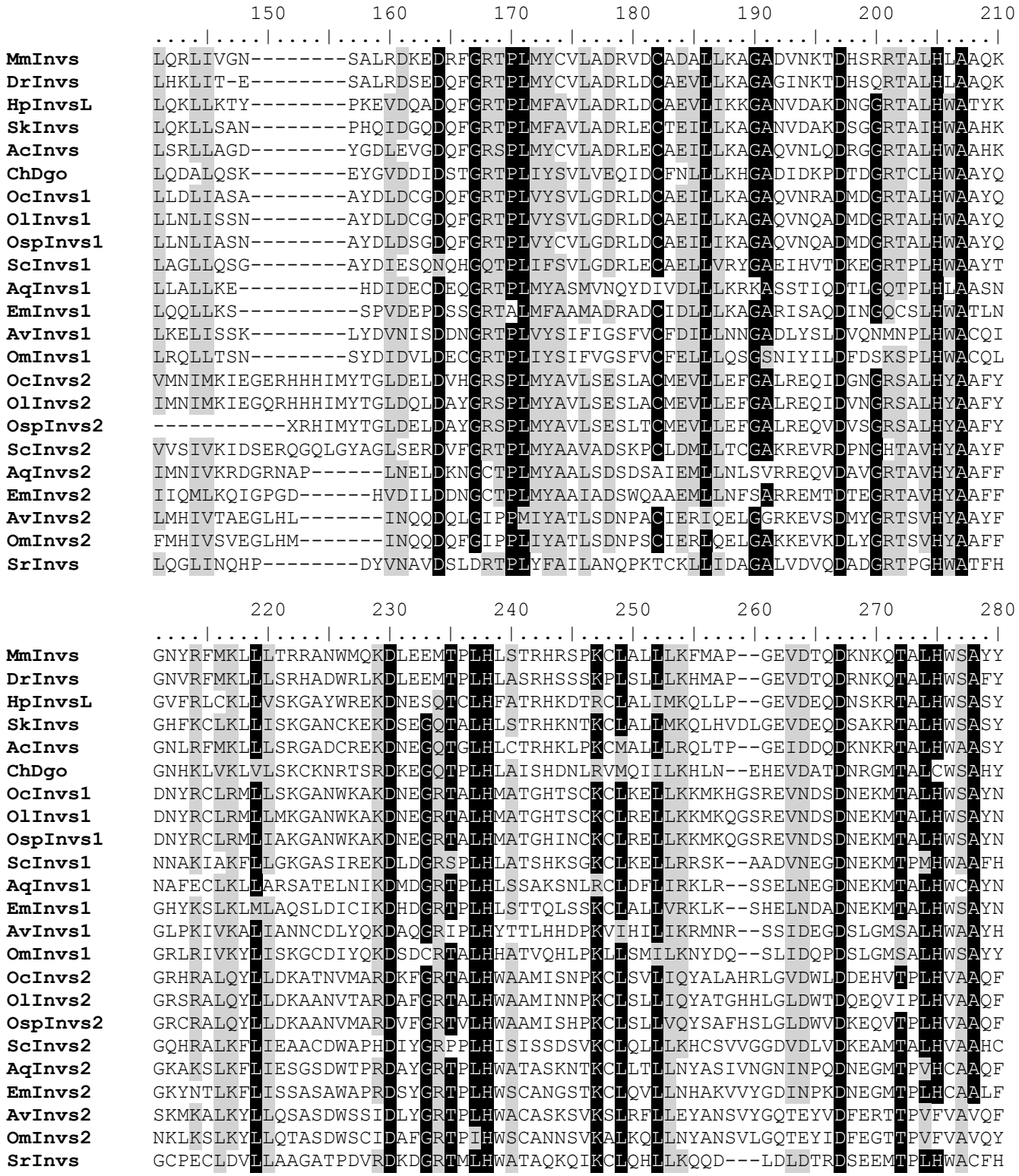


Abbreviations. Vertebrate: Dr, *Danio rerio;* Lc, Latimeria chalumnae and Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Ambulacraria. Sp, *Strongylocentrotus purpuratus*. Cnidaria: Ch, *Clytia hemisphaerica;* Nv, *Nematostella vectensis.* Placozoa: Ta, *Trichoplax adhaerens*. Porifera: Aq, *Amphimedon queenslandica*; Av, *Aphrocalistes vastus*; Em, *Ephydatia muelleri*; *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; *Om, Oopsacas minuta*; *Osp, Oscarella sp.*; Sc, *Sycon ciliatum*. Ctenophora: Ml, *Mnemiopsis leidyi*. Choanoflagellata: Sr, *Salpingoeca rosetta*.

Figure S2.4: Inversin alignment. Threshold for shading has been fixed at 80% for both identity (black) and similarity (grey). The black square indicate the C-terminal sequence shared by Ambulacraria, Mollusca and poriferan Invs 1 while the red squares correspond to the four AAX9Y/F motifs.

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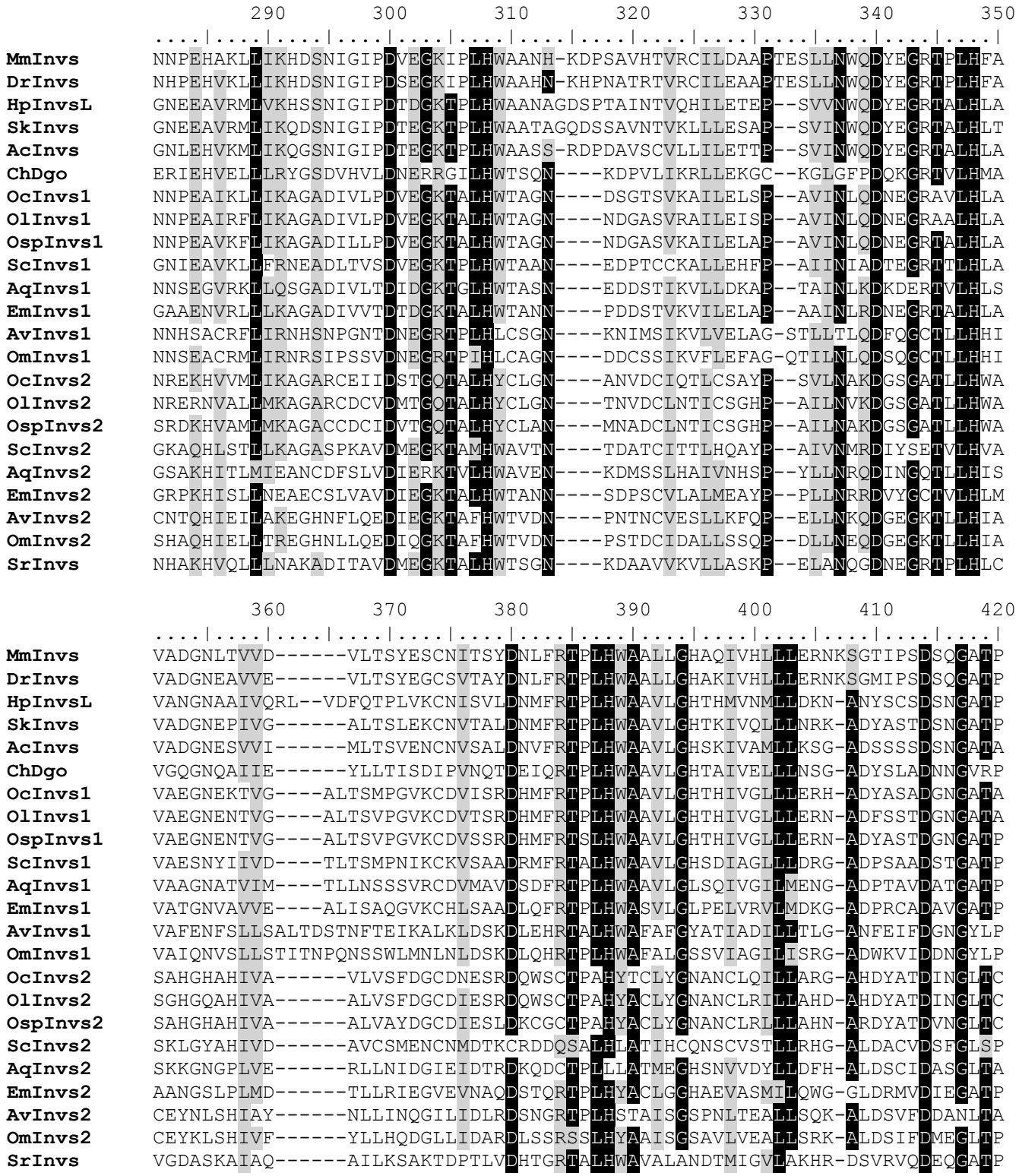
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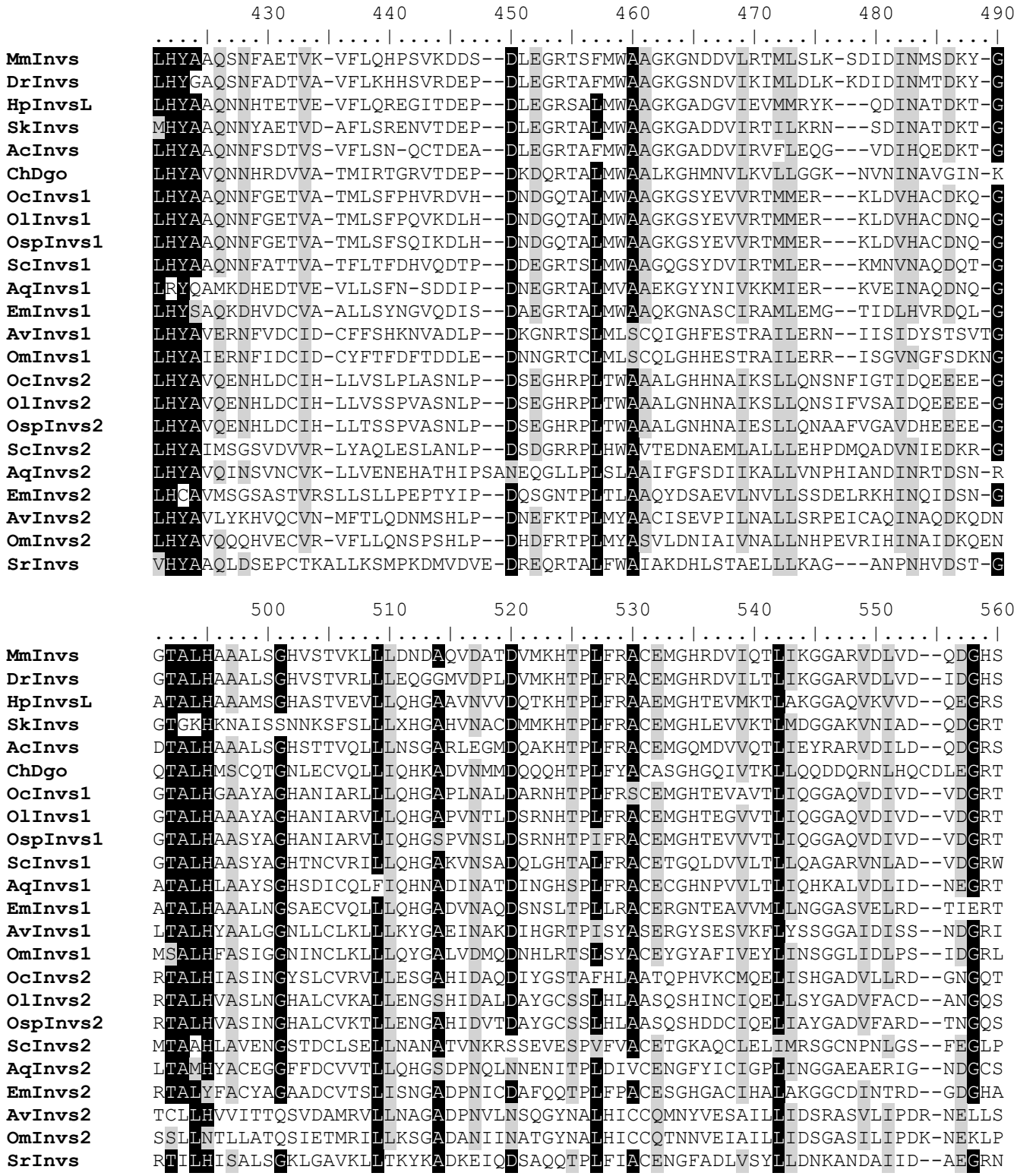
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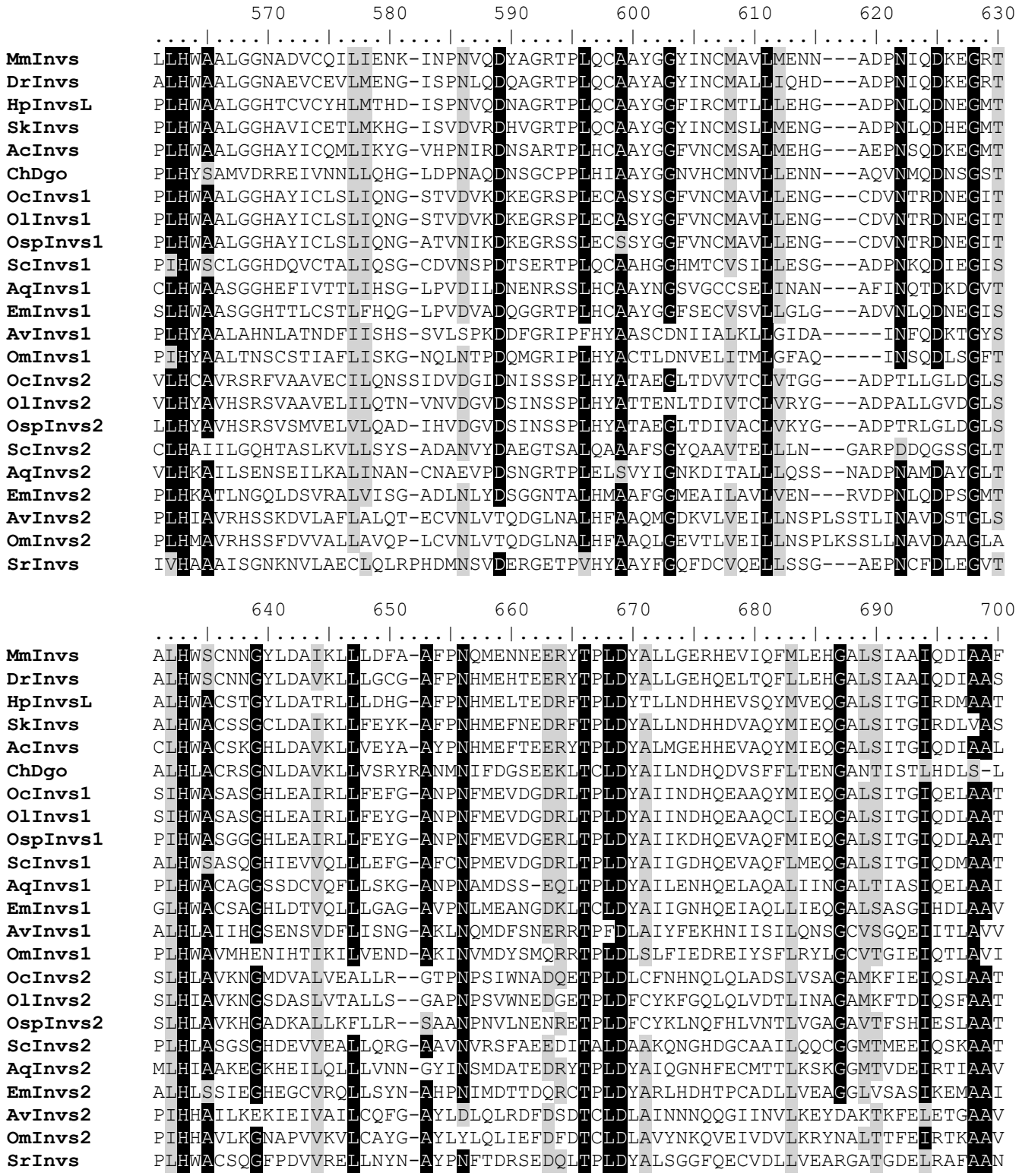
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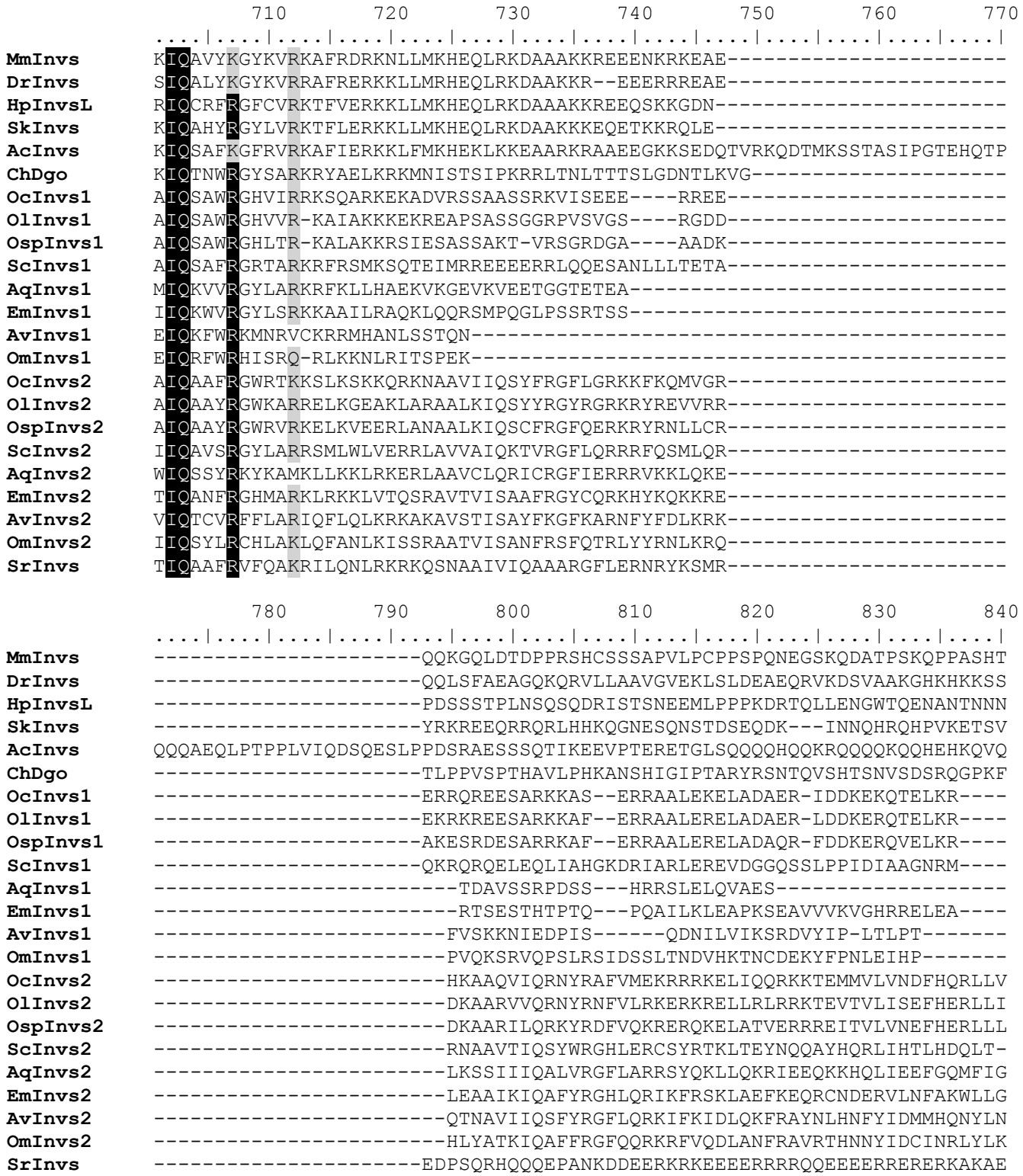
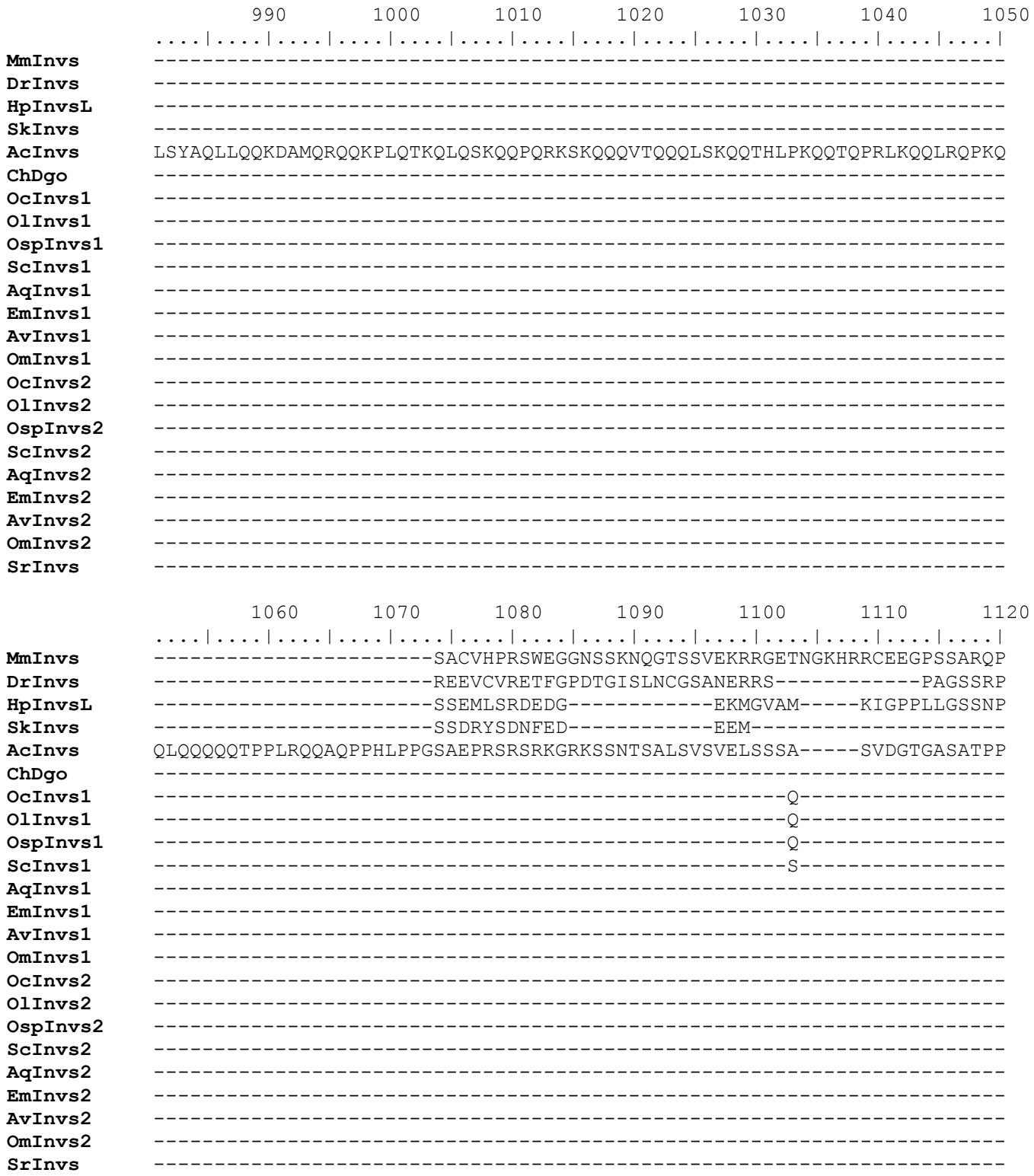
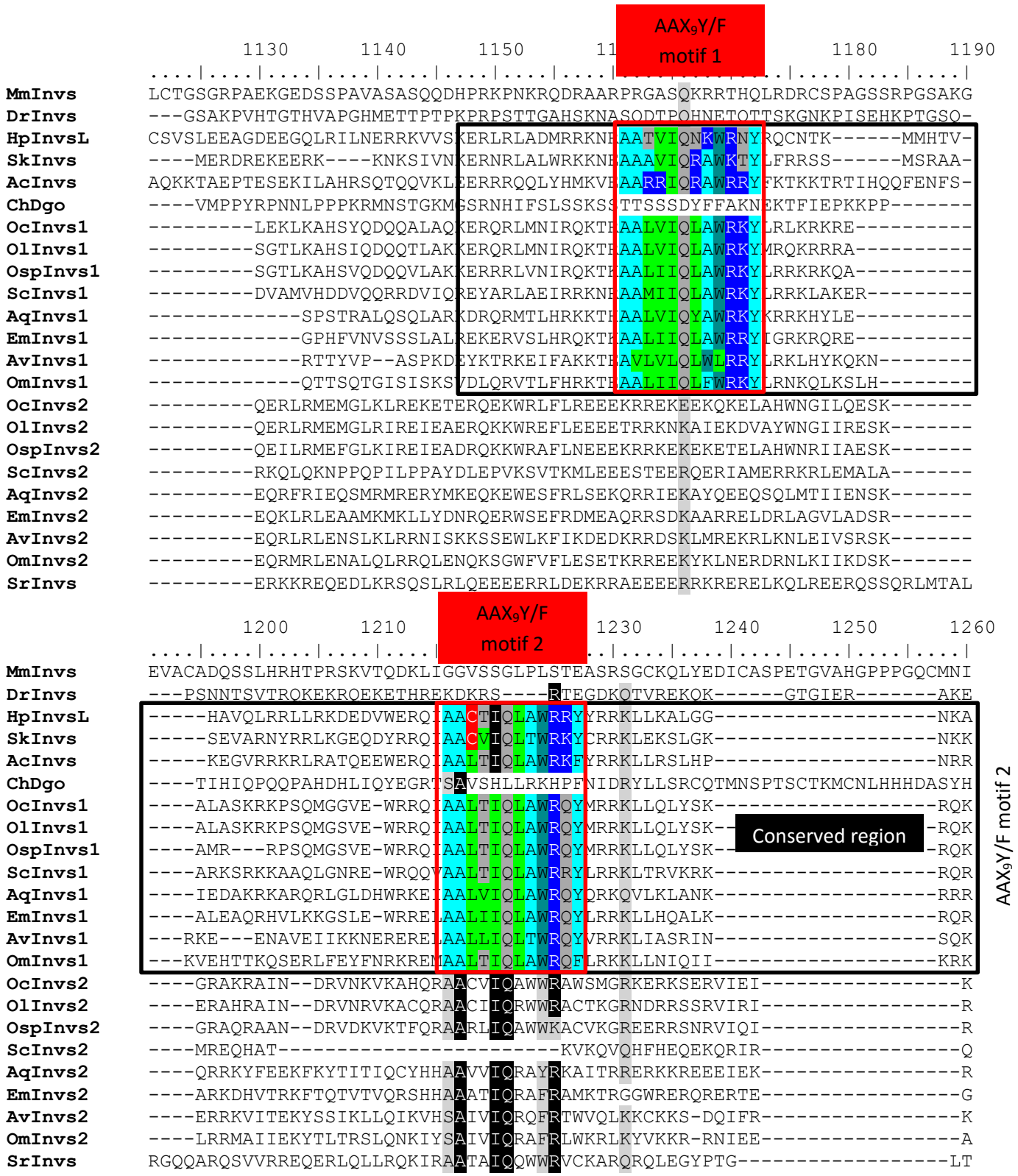
AcInvs PLHWAALGGHAYICQMLIKYG-VHPNIRDNSARTPLHCAAYGGFVNCMSALMEHG---AEPNSQDKEGMT
ChDgo PLHYSAMVDRREIVNNLLQHG-LDPNAQDNSGCPPLHIAAYGGNVHCMNVLLENN---AQVNMQDNSGST
OcInvs1 PLHWAALGGHAYICLSLIQNG-STVDVKDKEGRSPLECASYSGFVNCMAVLLENG---CDVNTRDNEGIT
OlInvs1 PLHWAALGGHAYICLSLIQNG-STVDVKDKEGRSPLECASYGGFVNCMAVLLENG---CDVNTRDNEGIT
OspInvs1 PLHWAALGGHAYICLSLIQNG-ATVNIKDKEGRSSLECSSYGGFVNCMAVLLENG---CDVNTRDNEGIT
ScInvs1 PIHWSCLGGHDQVCTALIQSG-CDVNSPDTSERTPLQCAAHGGHMTCVSILLESG---ADPNKQDIEGIS
AqInvs1 CLHWAASGGHEFIVTTLIHSG-LPVDILDNENRSSLHCAAYNGSVGCCSELINAN---AFINQTDKDGVT
EmInvs1 SLHWAASGGHTTLCSTLFHQG-LPVDVADQGGRTPLHCAAYGGFSECVSVLLGLG---ADVNLQDNEGIS
AvInvs1 PLHYAALAHNLATNDFIISHS-SVLSPKDDFGRIPFHYAASCDNIIALKLLGIDA-----INFQDKTGYS
OmInvs1 PIHYAALTNSCSTIAFLISKG-NQLNTPDQMGRIPLHYACTLDNVELITMLGFAQ-----INSQDLSGFT
OcInvs2 VLHCAVRSRFVAAVECILQNSSIDVDGIDNISSSPLHYATAEGLTDVVTCLVTGG---ADPTLLGLDGLS
OlInvs2 VLHYAVHSRSVAAVELILQTN-VNVDGVDSINSSPLHYATTENLTDIVTCLVRYG---ADPALLGVDGLS
OspInvs2 LLHYAVHSRSVSMVELVLQAD-IHVDGVDSINSSPLHYATAEGLTDIVACLVKYG---ADPTRLGLDGLS
ScInvs2 CLHAIILGQHTASLKVLLSYS-ADANVYDAEGTSALQAAAFSGYQAAVTELLLN---GARPDDQGSSGLT
AqInvs2 VLHKAILSENSEILKALINAN-CNAEVPDSNGRTPLELSVYIGNKDITALLLQSS--NADPNAMDAYGLT
EmInvs2 PLHKATLNGQLDSVRALVISG-ADLNLYDSGGNTALHMAAFGGMEAILAVLVEN---RVDPNLQDPSGMT
AvInvs2 PLHIAVRHSSKDVLAFLALQT-ECVNLVTQDGLNALHFAAQMGDKVLVEILLNSPLSSTLINAVDSTGLS
OmInvs2 PLHMAVRHSSFDVVALLAVQP-LCVNLVTQDGLNALHFAAQLGEVTLVEILLNSPLKSSLLNAVDAAGLA
SrInvs IVHAAAISGNKNVLAECLQLRPHDMNSVDERGETPVHYAAYFGQFDCVQELLSSG---AEPNCFDLEGVT
640 650 660 670 680 690 700
MmInvs ALHWSCNNGYLDAIKLLLDFA-AFPNQMENNEERYTPLDYALLGERHEVIQFMLEHGALSIAAIQDIAAF
DrInvs ALHWSCNNGYLDAVKLLLGCG-AFPNHMEHTEERYTPLDYALLGEHQELTQFLLEHGALSIAAIQDIAAS
HpInvsL ALHWACSTGYLDATRLLLDHG-AFPNHMELTEDRFTPLDYTLLNDHHEVSQYMVEQGALSITGIRDMAAT
SkInvs ALHWACSSGCLDAIKLLFEYK-AFPNHMEFNEDRFTPLDYALLNDHHDVAQYMIEQGALSITGIRDLVAS
AcInvs CLHWACSKGHLDAVKLLVEYA-AYPNHMEFTEERYTPLDYALMGEHHEVAQYMIEQGALSITGIQDIAAL
ChDgo ALHLACRSGNLDAVKLLVSRYRANMNIFDGSEEKLTCLDYAILNDHQDVSFFLTENGANTISTLHDLS-L
OcInvs1 SIHWASASGHLEAIRLLFEFG-ANPNFMEVDGDRLTPLDYAIINDHQEAAQYMIEQGALSITGIQELAAT
OlInvs1 SIHWASASGHLEAIRLLFEYG-ANPNFMEVDGDRLTPLDYAIINDHQEAAQCLIEQGALSITGIQDLAAT
OspInvs1 PIHWASGGGHLEAIRLLFEYG-ANPNFMEVDGERLTPLDYAIIKDHQEVAQFMIEQGALSITGIQDLAAT
ScInvs1 ALHWSASQGHIEVVQLLLEFG-AFCNPMEVDGDRLTPLDYAIIGDHQEVAQFLMEQGALSITGIQDMAAT
AqInvs1 PLHWACAGGSSDCVQFLLSKG-ANPNAMDSS-EQLTPLDYAILENHQELAQALIINGALTIASIQELAAI
EmInvs1 GLHWACSAGHLDTVQLLLGAG-AVPNLMEANGDKLTCLDYAIIGNHQEIAQLLIEQGALSASGIHDLAAV
AvInvs1 ALHLAIIHGSENSVDFLISNG-AKLNQMDFSNERRTPFDLAIYFEKHNIISILQNSGCVSGQEIITLAVV
OmInvs1 PLHWAVMHENIHTIKILVEND-AKINVMDYSMQRRTPLDLSLFIEDREIYSFLRYLGCVTGIEIQTLAVI
OcInvs2 SLHLAVKNGMDVALVEALLR--GTPNPSIWNADQETPLDLCFNHNQLQLADSLVSAGAMKFIEIQSLAAT
OlInvs2 SLHIAVKNGSDASLVTALLS--GAPNPSVWNEDGETPLDFCYKFGQLQLVDTLINAGAMKFTDIQSFAAT
OspInvs2 SLHLAVKHGADKALLKFLLR--SAANPNVLNENRETPLDFCYKLNQFHLVNTLVGAGAVTFSHIESLAAT
ScInvs2 PLHLASGSGHDEVVEALLQRG-AAVNVRSFAEEDITALDAAKQNGHDGCAAILQQCGGMTMEEIQSKAAT
AqInvs2 MLHIAAKEGKHEILQLLLVNN-GYINSMDATEDRYTPLDYAIQGNHFECMTTLKSKGGMTVDEIRTIAAV
EmInvs2 ALHLSSIEGHEGCVRQLLSYN-AHPNIMDTTDQRCTPLDYARLHDHTPCADLLVEAGGLVSASIKEMAAI
AvInvs2 PIHHAILKEKIEIVAILCQFG-AYLDLQLRDFDSDTCLDLAINNNQQGIINVLKEYDAKTKFELETGAAV
OmInvs2 PIHHAVLKGNAPVVKVLCAYG-AYLYLQLIEFDFDTCLDLAVYNKQVEIVDVLKRYNALTTFEIRTKAAV
SrInvs PLHWACSQGFPDVVRELLNYN-AYPNFTDRSEDQLTPLDYALSGGFQECVDLLVEARGATGDELRAFAAN

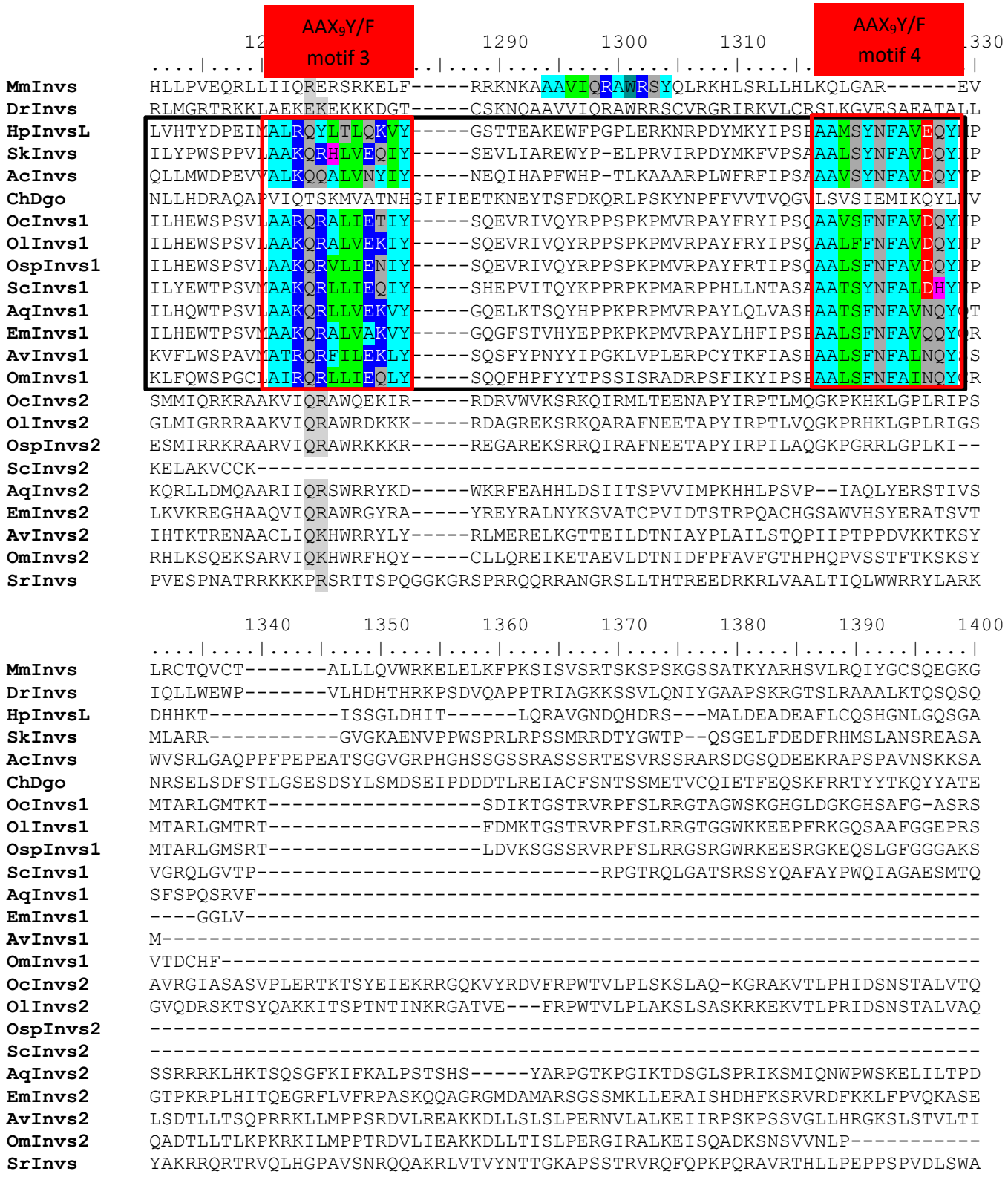

710 720 730 740 750 760 770
MmInvs KIQAVYKGYKVRKAFRDRKNLLMKHEQLRKDAAAKKREEENKRKEAE----------
DrInvs SIQALYKGYKVRRAFRERKKLLMRHEQLRKDAAKKR--EEERRREAE----------
HpInvsL RIQCRFRGFCVRKTFVERKKLLMKHEQLRKDAAAKKREEQSKKGDN----------
SkInvs KIQAHYRGYLVRKTFLERKKLLMKHEQLRKDAAKKKEQETKKRQLE----------
AcInvs KIQSAFKGFRVRKAFIERKKLFMKHEKLKKEAARKRAAEEGKKSEDQTVRKQDTMKSSTASIPGTEHQTP
ChDgo KIQTNWRGYSARKRYAELKRKMNISTSIPKRRLTNLTTTSLGDNTLKVG----------
OcInvs1 AIQSAWRGHVIRRKSQARKEKADVRSSAASSRKVISEEE----RREE----------
OlInvs1 AIQSAWRGHVVR-KAIAKKKEKREAPSASSGGRPVSVGS----RGDD----------
OspInvs1 AIQSAWRGHLTR-KALAKKRSIESASSAKT-VRSGRDGA----AADK----------
ScInvs1 AIQSAFRGRTARKRFRSMKSQTEIMRREEEERRLQQESANLLLTETA----------
AqInvs1 MIQKVVRGYLARKRFKLLHAEKVKGEVKVEETGGTETEA----------
EmInvs1 IIQKWVRGYLSRKKAAILRAQKLQQRSMPQGLPSSRTSS----------
AvInvs1 EIQKFWRKMNRVCKRRMHANLSSTQN----------
OmInvs1 EIQRFWRHISRQ-RLKKNLRITSPEK----------
OcInvs2 AIQAAFRGWRTKKSLKSKKQRKNAAVIIQSYFRGFLGRKKFKQMVGR----------
OlInvs2 AIQAAYRGWKARRELKGEAKLARAALKIQSYYRGYRGRKRYREVVRR----------
OspInvs2 AIQAAYRGWRVRKELKVEERLANAALKIQSCFRGFQERKRYRNLLCR----------
ScInvs2 IIQAVSRGYLARRSMLWLVERRLAVVAIQKTVRGFLQRRRFQSMLQR----------
AqInvs2 WIQSSYRKYKAMKLLKKLRKERLAAVCLQRICRGFIERRRVKKLQKE----------
EmInvs2 TIQANFRGHMARKLRKKLVTQSRAVTVISAAFRGYCQRKHYKQKKRE----------
AvInvs2 VIQTCVRFFLARIQFLQLKRKAKAVSTISAYFKGFKARNFYFDLKRK----------
OmInvs2 IIQSYLRCHLAKLQFANLKISSRAATVISANFRSFQTRLYYRNLKRQ----------
SrInvs TIQAAFRVFQAKRILQNLRKRKQSNAAIVIQAAARGFLERNRYKSMR----------
780 790 800 810 820 830 840
MmInvs ----------QQKGQLDTDPPRSHCSSSAPVLPCPPSPQNEGSKQDATPSKQPPASHT
DrInvs ----------QQLSFAEAGQKQRVLLAAVGVEKLSLDEAEQRVKDSVAAKGHKHKKSS
HpInvsL ----------PDSSSTPLNSQSQDRISTSNEEMLPPPKDRTQLLENGWTQENANTNNN
SkInvs ----------YRKREEQRRQRLHHKQGNESQNSTDSEQDK---INNQHRQHPVKETSV
AcInvs QQQAEQLPTPPLVIQDSQESLPPDSRAESSSQTIKEEVPTERETGLSQQQQHQQKRQQQQKQQHEHKQVQ
ChDgo ----------TLPPVSPTHAVLPHKANSHIGIPTARYRSNTQVSHTSNVSDSRQGPKF
OcInvs1 ----------ERRQREESARKKAS--ERRAALEKELADAER-IDDKEKQTELKR----
OlInvs1 ----------EKRKREESARKKAF--ERRAALERELADAER-LDDKERQTELKR----
OspInvs1 ----------AKESRDESARRKAF--ERRAALERELADAQR-FDDKERQVELKR----
ScInvs1 ----------QKRQRQELEQLIAHGKDRIARLEREVDGGQSSLPPIDIAAGNRM----
AqInvs1 ----------TDAVSSRPDSS---HRRSLELQVAES----------
EmInvs1 ----------RTSESTHTPTQ---PQAILKLEAPKSEAVVVKVGHRRELEA----
AvInvs1 ----------FVSKKNIEDPIS------QDNILVIKSRDVYIP-LTLPT-------
OmInvs1 ----------PVQKSRVQPSLRSIDSSLTNDVHKTNCDEKYFPNLEIHP-------
OcInvs2 ----------HKAAQVIQRNYRAFVMEKRRRKELIQQRKKTEMMVLVNDFHQRLLV
OlInvs2 ----------DKAARVVQRNYRNFVLRKERKRELLRLRRKTEVTVLISEFHERLLI
OspInvs2 ----------DKAARILQRKYRDFVQKRERQKELATVERRREITVLVNEFHERLLL
ScInvs2 ----------RNAAVTIQSYWRGHLERCSYRTKLTEYNQQAYHQRLIHTLHDQLT-
AqInvs2 ----------LKSSIIIQALVRGFLARRSYQKLLQKRIEEQKKHQLIEEFGQMFIG
EmInvs2 ----------LEAAIKIQAFYRGHLQRIKFRSKLAEFKEQRCNDERVLNFAKWLLG
AvInvs2 ----------QTNAVIIQSFYRGFLQRKIFKIDLQKFRAYNLHNFYIDMMHQNYLN
OmInvs2 ----------HLYATKIQAFFRGFQQRKRFVQDLANFRAVRTHNNYIDCINRLYLK
SrInvs ----------EDPSQRHQQQEPANKDDEERKRKEEEERRRRQQEEEERRERERKAKAE

```
                 850       860       870       880       890       900       910
            ....|....|....|....|....|....|....|....|....|....|....|....|....|....|
MmInvs      VQSPDPEHSRLPGRCPGRASQGDSSIDLQGTASRKPSETPIEHCRGP----------------------
DrInvs      SAHNSQSRREKPSRAERRTREPETSDAPSIRSLPPVTPMSTKKCPVT----------------------
HpInvsL     ----------------------NNSAVDASVN--LSEGFAP----------------------------
SkInvs      ----------------------TSSDTEESVSSSRSDKYSV----------------------------
AcInvs      PQLQREERGEDPVAVNGKTLTSASSDSDSGAVTGSSSTVSSQGRRKHTQLQQQQQPASQKDIVVEKKKSP
ChDgo       IEGN---------AANPFSLNRVARVKSPGTEMRVPNSSRSKSSTG----------------------
OcInvs1     ----------------------RQRQLDHEERLREESARQPDSPKN----------------------
OlInvs1     ----------------------RQRQLEQEERLR---ERQQGSPRRY----------------------
OspInvs1    ----------------------RQRQLEQEERLR---LSE--SPKR----------------------
ScInvs1     ----------------------VKASKDKGKGVRLPPISQHGQLTS----------------------
AqInvs1     -------------------------ERQAKEWALR-----------------------------------
EmInvs1     ----------------------RLKETDQKLQSLS-----------------------------------
AvInvs1     ------------------------------------------------------------------------
OmInvs1     ------------------------------------------------------------------------
OcInvs2     DK-----------------AKAKVKSEKGNGMEEKKENVIPDQMKLN----------------------
OlInvs2     DR-----------------ARVKAKPIVD---RKGGEDSDKEKAVSN----------------------
OspInvs2    DK-----------------RLVKAKPTVE---ERRRDK--EEKARFN----------------------
ScInvs2     -------------------------QKWRQEGLTRTPPKAQPPVQT----------------------
AqInvs2     ------------------LQRIEPIVIDADELHMKAKDKDHEGAKK----------------------
EmInvs2     VGAG-DLTALAESERAPPPQPSFMSGHELRGAGIQSESACTAQDVRV----------------------
AvInvs2     EIANSKFKKLTIEDLDFENSLFISPWRSSLREKRQETLDDRSRRLEN----------------------
OmInvs2     GIRENTIKTFTIKDLDFTDALYISPWRSSLREKRQETVEDRIRRLEN----------------------
SrInvs      QE-----------------EKLRKKKQKQEQERRRREEARKKKEAE----------------------

                 920       930       940       950       960       970       980
            ....|....|....|....|....|....|....|....|....|....|....|....|....|....|
MmInvs      ------------------------------------------------------------------------
DrInvs      ------------------------------------------------------------------------
HpInvsL     ------------------------------------------------------------------------
SkInvs      ------------------------------------------------------------------------
AcInvs      DPLTVEVQKKSLMPAPAPVTTLPKQDEPTRRQQQTVGTPDVKPKQRSRSGGRLQERGHSAPPRRSSKPIA
ChDgo       ------------------------------------------------------------------------
OcInvs1     ------------------------------------------------------------------------
OlInvs1     ------------------------------------------------------------------------
OspInvs1    ------------------------------------------------------------------------
ScInvs1     ------------------------------------------------------------------------
AqInvs1     ------------------------------------------------------------------------
EmInvs1     ------------------------------------------------------------------------
AvInvs1     ------------------------------------------------------------------------
OmInvs1     ------------------------------------------------------------------------
OcInvs2     ------------------------------------------------------------------------
OlInvs2     ------------------------------------------------------------------------
OspInvs2    ------------------------------------------------------------------------
ScInvs2     ------------------------------------------------------------------------
AqInvs2     ------------------------------------------------------------------------
EmInvs2     ------------------------------------------------------------------------
AvInvs2     ------------------------------------------------------------------------
OmInvs2     ------------------------------------------------------------------------
SrInvs      ------------------------------------------------------------------------
```


990 1000 1010 1020 1030 1040 1050
MmInvs
DrInvs
HpInvsL
SkInvs
AcInvs LSYAQLLQQKDAMQRQQKPLQTKQLQSKQQPQRKSKQQQVTQQQLSKQQTHLPKQQTQPRLKQQLRQPKQ
ChDgo
OcInvs1
OlInvs1
OspInvs1
ScInvs1
AqInvs1
EmInvs1
AvInvs1
OmInvs1
OcInvs2
OlInvs2
OspInvs2
ScInvs2
AqInvs2
EmInvs2
AvInvs2
OmInvs2
SrInvs
1060 1070 1080 1090 1100 1110 1120
MmInvs ----------SACVHPRSWEGGNSSKNQGTSSVEKRRGETNGKHRRCEEGPSSARQP
DrInvs ----------REEVCVRETFGPDTGISLNCGSANERRS----------PAGSSRP
HpInvsL ----------SSEMLSRDEDG----------EKMGVAM-----KIGPPLLGSSNP
SkInvs ----------SSDRYSDNFED----------EEM----------
AcInvs QLQQQQQTPPLRQQAQPPHLPPGSAEPRSRSRKGRKSSNTSALSVSVELSSSA-----SVDGTGASATPP
ChDgo
OcInvs1 ----------Q----------
OlInvs1 ----------Q----------
OspInvs1 ----------Q----------
ScInvs1 ----------S----------
AqInvs1
EmInvs1
AvInvs1
OmInvs1
OcInvs2
OlInvs2
OspInvs2
ScInvs2
AqInvs2
EmInvs2
AvInvs2
OmInvs2
SrInvs


AAX9Y/F motif 1
AAX9Y/F motif 2
Conserved region
AAX9Y/F motif 2


AAX9Y/F
motif 3
AAX9Y/F
motif 4
1290
1300
1310
1330
MmInvs
DrInvs
HpInvsL
SkInvs
AcInvs
ChDgo
OcInvs1
OlInvs1
OspInvs1
ScInvs1
AqInvs1
EmInvs1
AvInvs1
OmInvs1
OcInvs2
OlInvs2
OspInvs2
ScInvs2
AqInvs2
EmInvs2
AvInvs2
OmInvs2
SrInvs
1340
1350
1360
1370
1380
1390
1400
MmInvs
DrInvs
HpInvsL
SkInvs
AcInvs
ChDgo
OcInvs1
OlInvs1
OspInvs1
ScInvs1
AqInvs1
EmInvs1
AvInvs1
OmInvs1
OcInvs2
OlInvs2
OspInvs2
ScInvs2
AqInvs2
EmInvs2
AvInvs2
OmInvs2
SrInvs

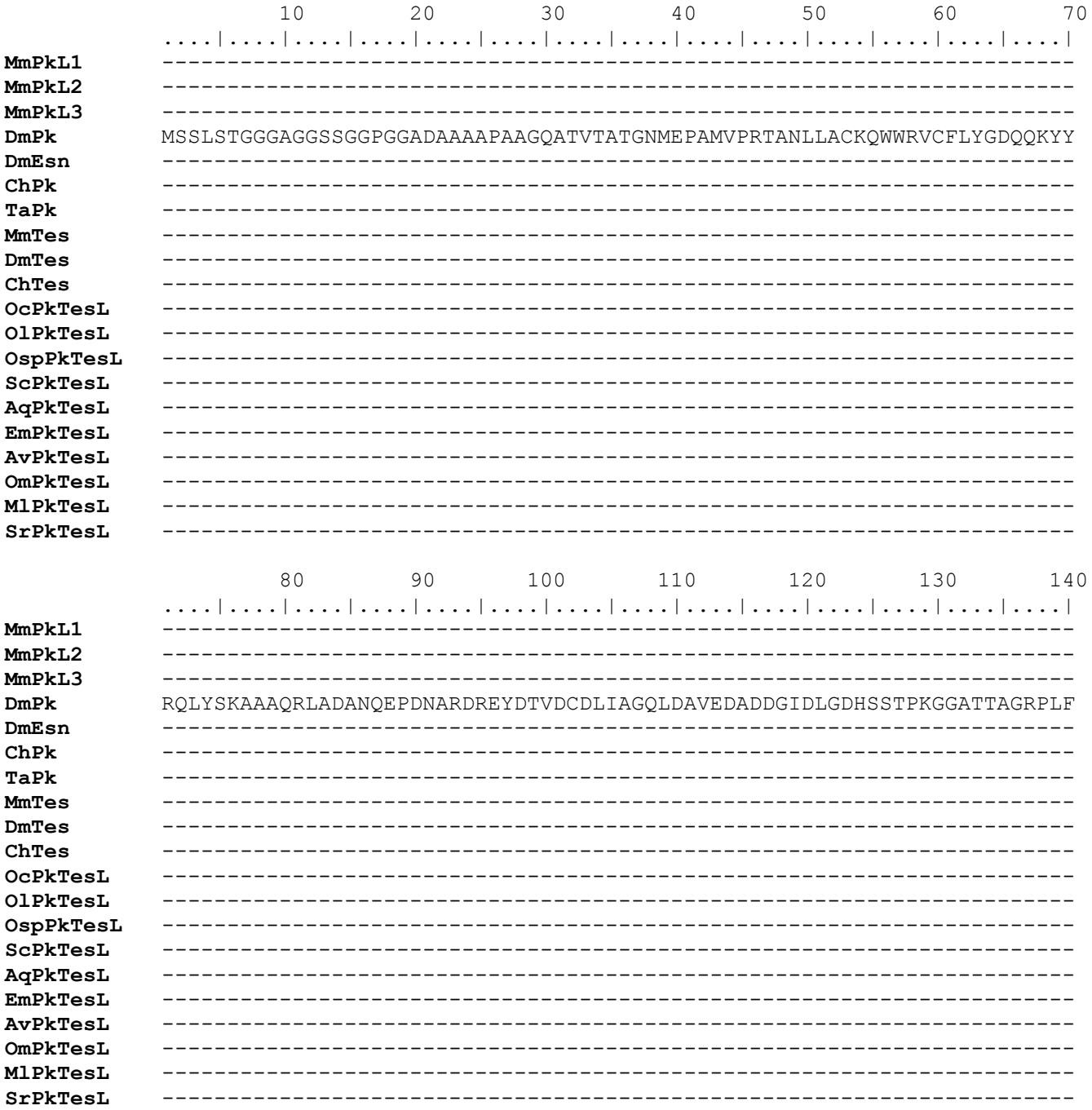
```
                1410      1420      1430      1440      1450      1460      1470
           ....|....|....|....|....|....|....|....|....|....|....|....|....|....|
MmInvs     HHPIKSSKAPAVLHLSSVNSLQSIHLDNSGRSKKFSYNLQPSSQSKNKPKL-----------------
DrInvs     SQVLLDLSLRTHKQLSAVECVN--LVDSVSQAKQFSYHLRPSSGASQSSQN-----------------
HpInvsL    P-YSYNLND-------------------------------------------------------------
SkInvs     DHFSYNLHR-------------------------------------------------------------
AcInvs     LSSSNTKKKS-------------------------------------------------------------
ChDgo      LFICLKTKTFSKSRKFYYFIEWKGSLEGRYENEKNNRISIYRLDFARCYWCGSEFTEEAEKSQTGSFIFL
OcInvs1    VAGSILF----------------------------------------------------------------
OlInvs1    LASSVLF----------------------------------------------------------------
OspInvs1   IASSVIF----------------------------------------------------------------
ScInvs1    QFQVLDFN---------------------------------------------------------------
AqInvs1    ----------------------------------------------------------------------
EmInvs1    ----------------------------------------------------------------------
AvInvs1    ----------------------------------------------------------------------
OmInvs1    ----------------------------------------------------------------------
OcInvs2    K----------------------------------------------------------------------
OlInvs2    K----------------------------------------------------------------------
OspInvs2   ----------------------------------------------------------------------
ScInvs2    ----------------------------------------------------------------------
AqInvs2    ETNEESLKLPNIMLRQHTGHRSNNPLAMTPIKLPLLK---------------------------------
EmInvs2    TTRGSRSSERRIAVEQDPSQRGPSQRGHSQQGLSQRGPLQRGPSQQSHSQQGPSQQSRSQRGLPQLLKAL
AvInvs2    PLDSKIDPFRNFKSQIAHVRSEFELPDNLPHRNPETNRKSYVMKRANSLQILKTDSSLPFVGSETKQIPI
OmInvs2    VLDAEIPIC--------------------------------------------------------------
SrInvs     SAASTYFKPPNPGRRRPRGLHATRRRQRQPAYANMQDPEHMLTLPIIHGTQGSRKNDARLNQAVSLPPV-

                1480      1490      1500      1510      1520      1530      1540
           ....|....|....|....|....|....|....|....|....|....|....|....|....|....|
MmInvs     ----------------------------------------------------------------------
DrInvs     ----------------------------------------------------------------------
HpInvsL    ----------------------------------------------------------------------
SkInvs     ----------------------------------------------------------------------
AcInvs     ----------------------------------------------------------------------
ChDgo      PFDGKYLPKRASKTHKETIHEPFVTKTVHSNRDLQNEAALSQRRYTVQGRYRSIEKRKTKIIFKLERIDL
OcInvs1    ----------------------------------------------------------------------
OlInvs1    ----------------------------------------------------------------------
OspInvs1   ----------------------------------------------------------------------
ScInvs1    ----------------------------------------------------------------------
AqInvs1    ----------------------------------------------------------------------
EmInvs1    ----------------------------------------------------------------------
AvInvs1    ----------------------------------------------------------------------
OmInvs1    ----------------------------------------------------------------------
OcInvs2    ----------------------------------------------------------------------
OlInvs2    ----------------------------------------------------------------------
OspInvs2   ----------------------------------------------------------------------
ScInvs2    ----------------------------------------------------------------------
AqInvs2    ----------------------------------------------------------------------
EmInvs2    PTGIRKSYTAPVQLPLIVNHTQS-----------------------------------------------
AvInvs2    LTETKSSFTSLPPIVQK-----------------------------------------------------
OmInvs2    ----------------------------------------------------------------------
SrInvs     ----------------------------------------------------------------------
```

```
                1550
          ....|....|....
MmInvs    --------------
DrInvs    --------------
HpInvsL   --------------
SkInvs    --------------
AcInvs    --------------
ChDgo     YIYFVMNFSIDAFT
OcInvs1   --------------
OlInvs1   --------------
OspInvs1  --------------
ScInvs1   --------------
AqInvs1   --------------
EmInvs1   --------------
AvInvs1   --------------
OmInvs1   --------------
OcInvs2   --------------
OlInvs2   --------------
OspInvs2  --------------
ScInvs2   --------------
AqInvs2   --------------
EmInvs2   --------------
AvInvs2   --------------
OmInvs2   --------------
SrInvs    --------------
```

Abbreviations. Vertebrate: Dr, *Danio rerio* and Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Mollusca: Ac, *Aplysia californica* and Cg, *Crassotrea gigantea*. Ambulacraria: Hp, *Hemicentrotus pulcherrimus*; Sk and *Saccoglossus kowalevskii*. Cnidaria: Ch, *Clytia hemisphaerica.* Porifera: Aq, *Amphimedon queenslandica*; Av, *Aphrocalistes vastus*; Em, *Ephydatia muelleri*; *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; *Om, Oopsacas minuta*; *Osp, Oscarella sp*.; Sc, *Sycon ciliatum*. Choanoflagellata: Sr, *Salpingoeca rosetta*.

Figure S2.5: PET family alignment. Threshold for shading has been fixed at 80% for both identity (black) and similarity (grey).



```
                 150       160       170       180       190       200       210
            ....|....|....|....|....|....|....|....|....|....|....|....|....|....|
MmPkL1      ----------------------------------------------------------------------
MmPkL2      ----------------------------------------------------------------------
MmPkL3      ----------------------------------------------------------------------
DmPk        PHSSSPRRSKKLLRSLRAHVRGEKLPKNDTTTANESSEVTQRNARVTVLDDPFLFGIDADHLGDLVVRGK
DmEsn       ----------------------------------------------------------------------
ChPk        ----------------------------------------------------------------------
TaPk        ----------------------------------------------------------------------
MmTes       ----------------------------------------------------------------------
DmTes       ----------------------------------------------------------------------
ChTes       ----------------------------------------------------------------------
OcPkTesL    ----------------------------------------------------------------------
OlPkTesL    ----------------------------------------------------------------------
OspPkTesL   ----------------------------------------------------------------------
ScPkTesL    ----------------------------------------------------------------------
AqPkTesL    ----------------------------------------------------------------------
EmPkTesL    ----------------------------------------------------------------------
AvPkTesL    ----------------------------------------------------------------------
OmPkTesL    ----------------------------------------------------------------------
MlPkTesL    ----------------------------------------------------------------------
SrPkTesL    ----------------------------------------------------------------------

                 220       230       240       250       260       270       280
            ....|....|....|....|....|....|....|....|....|....|....|....|....|....|
MmPkL1      ----------------------------------------------------------------------
MmPkL2      ----------------------------------------------------------------------
MmPkL3      ----------------------------------------------------------------------
DmPk        RYSTLDATENMARFYAEQEATAQVLEIIEQEEESPEQEAPKPALPPKQKQQRPVPPLPPPPANRVTQDQG
DmEsn       ------------------------------------MQQAP-------QQQQHPHP----PSSSYYTQTES
ChPk        ----------------------------------------------------------------------
TaPk        ----------------------------------------------------------------------
MmTes       ----------------------------------------------------------------------
DmTes       ----------------------------------------------------------------------
ChTes       ----------------------------------------------------------------------
OcPkTesL    ----------------------------------------------------------------------
OlPkTesL    ----------------------------------------------------------------------
OspPkTesL   ----------------------------------------------------------------------
ScPkTesL    ----------------------------------------------------------------------
AqPkTesL    ----------------------------------------------------------------------
EmPkTesL    ----------------------------------------------------------------------
AvPkTesL    ----------------------------------------------------------------------
OmPkTesL    ----------------------------------------------------------------------
MlPkTesL    ----------------------------------------------------------------------
SrPkTesL    ----------------------------------------------------------------------
```

```
                290       300       310       320       330       340       350
           ....|....|....|....|....|....|....|....|....|....|....|....|....|....|
MmPkL1     ------------------------------------------------------------------------
MmPkL2     ------------------------------------------------------------------------
MmPkL3     ------------------------------------------------------------------------
DmPk       TQPAAPQVPLQPLTAGDLQFLNLSLRQRSLPRSMKPFKDAHDISFTFNELDTSAEPEVATGAAQQESNEP
DmEsn      --------ELLQIEAGGTGLTFASHSQRPES--------------AISQVASTAHLDVPSAASS------
ChPk       ------------------------------------------------------------------------
TaPk       ------------------------------------------------------------------------
MmTes      ------------------------------------------------------------------------
DmTes      ------------------------------------------------------------------------
ChTes      ------------------------------------------------------------------------
OcPkTesL   ------------------------------------------------------------------------
OlPkTesL   ------------------------------------------------------------------------
OspPkTesL  ------------------------------------------------------------------------
ScPkTesL   ------------------------------------------------------------------------
AqPkTesL   ------------------------------------------------------------------------
EmPkTesL   ------------------------------------------------------------------------
AvPkTesL   ------------------------------------------------------------------------
OmPkTesL   ------------------------------------------------------------------------
MlPkTesL   ------------------------------------------------------------------------
SrPkTesL   -------------------------------------------MEGSKKKKRVGVKFAAEAEVMVHEDP

                360       370       380       390       400       410       420
           ....|....|....|....|....|....|....|....|....|....|....|....|....|....|
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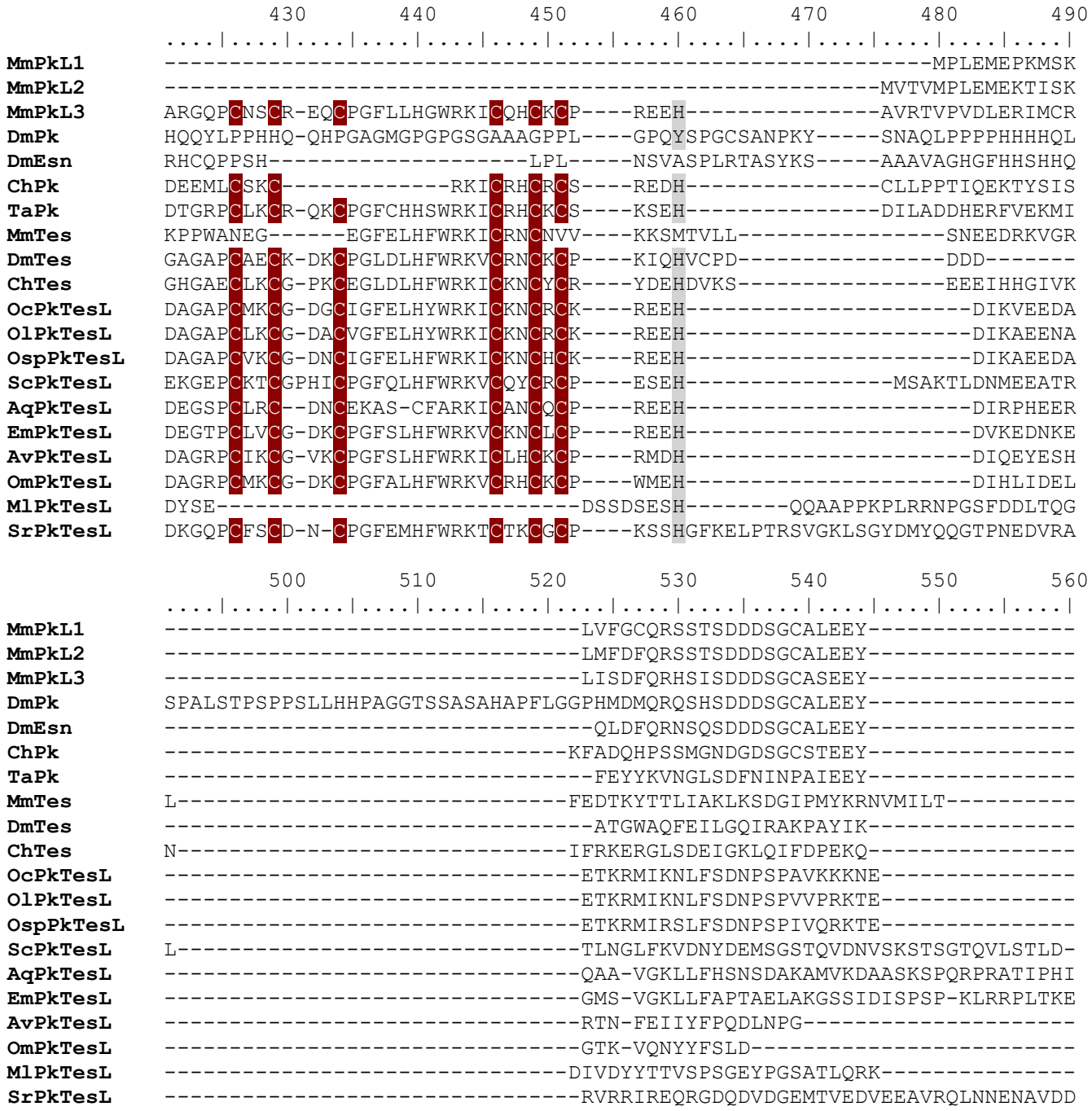
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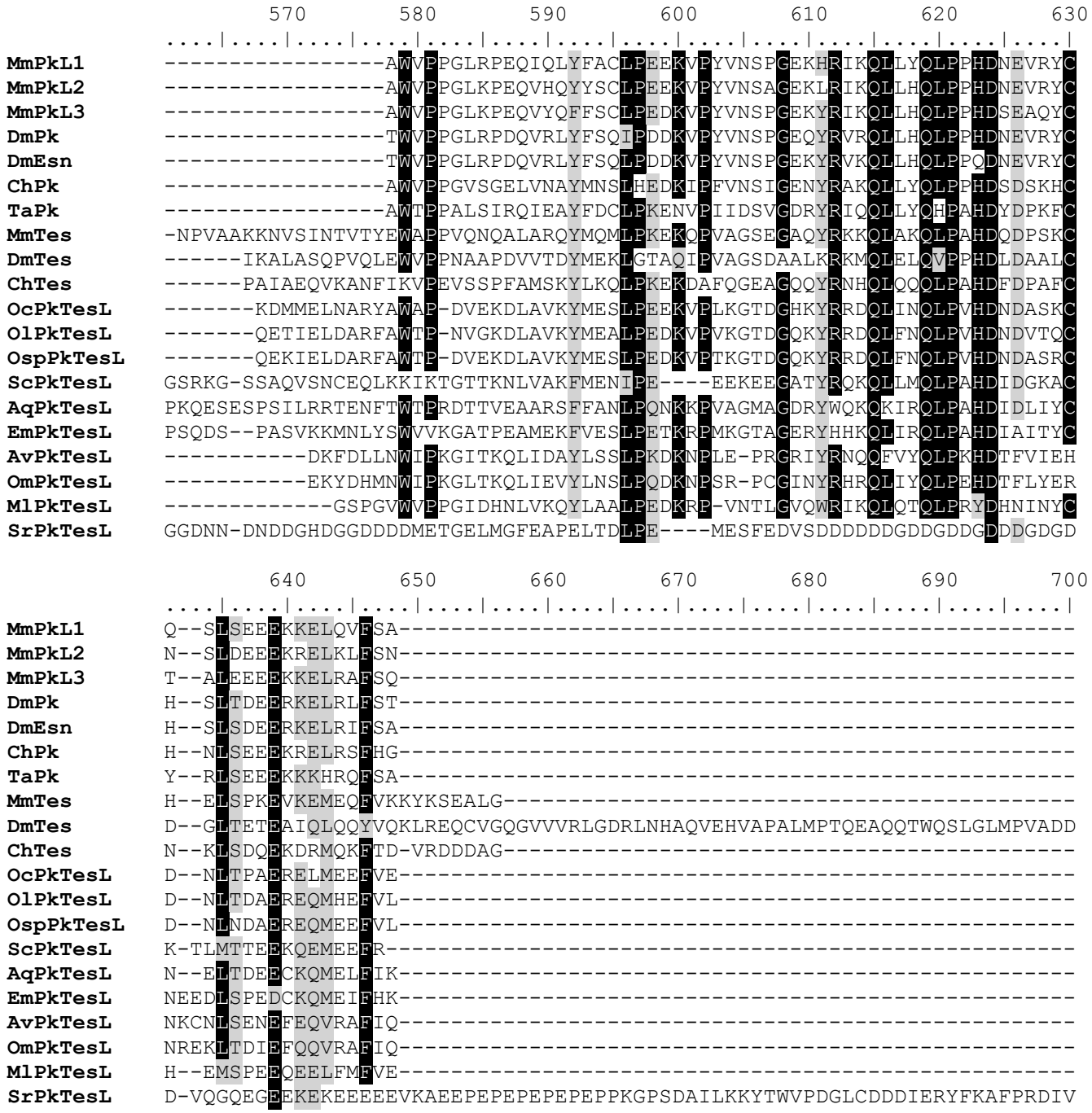
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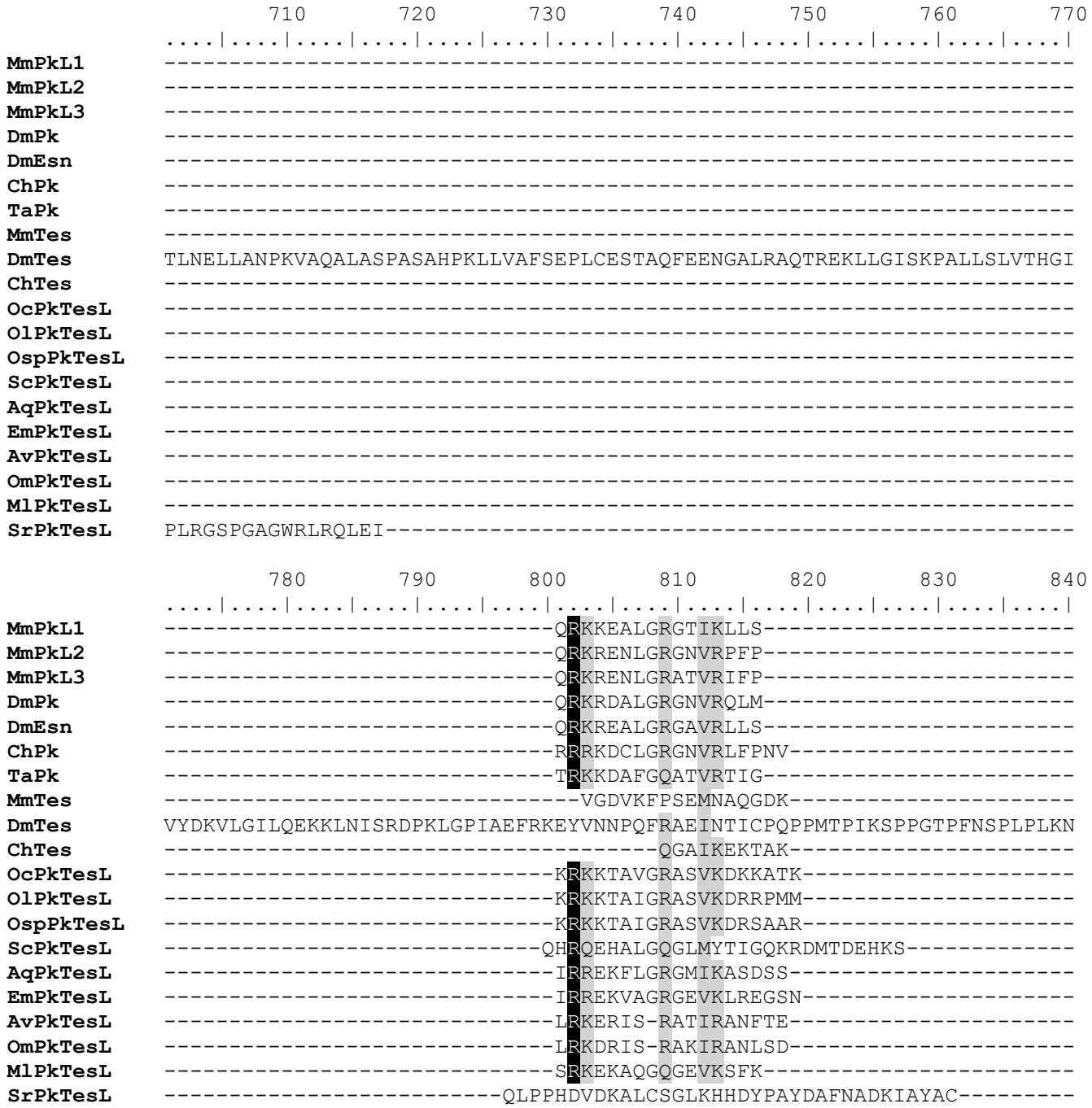
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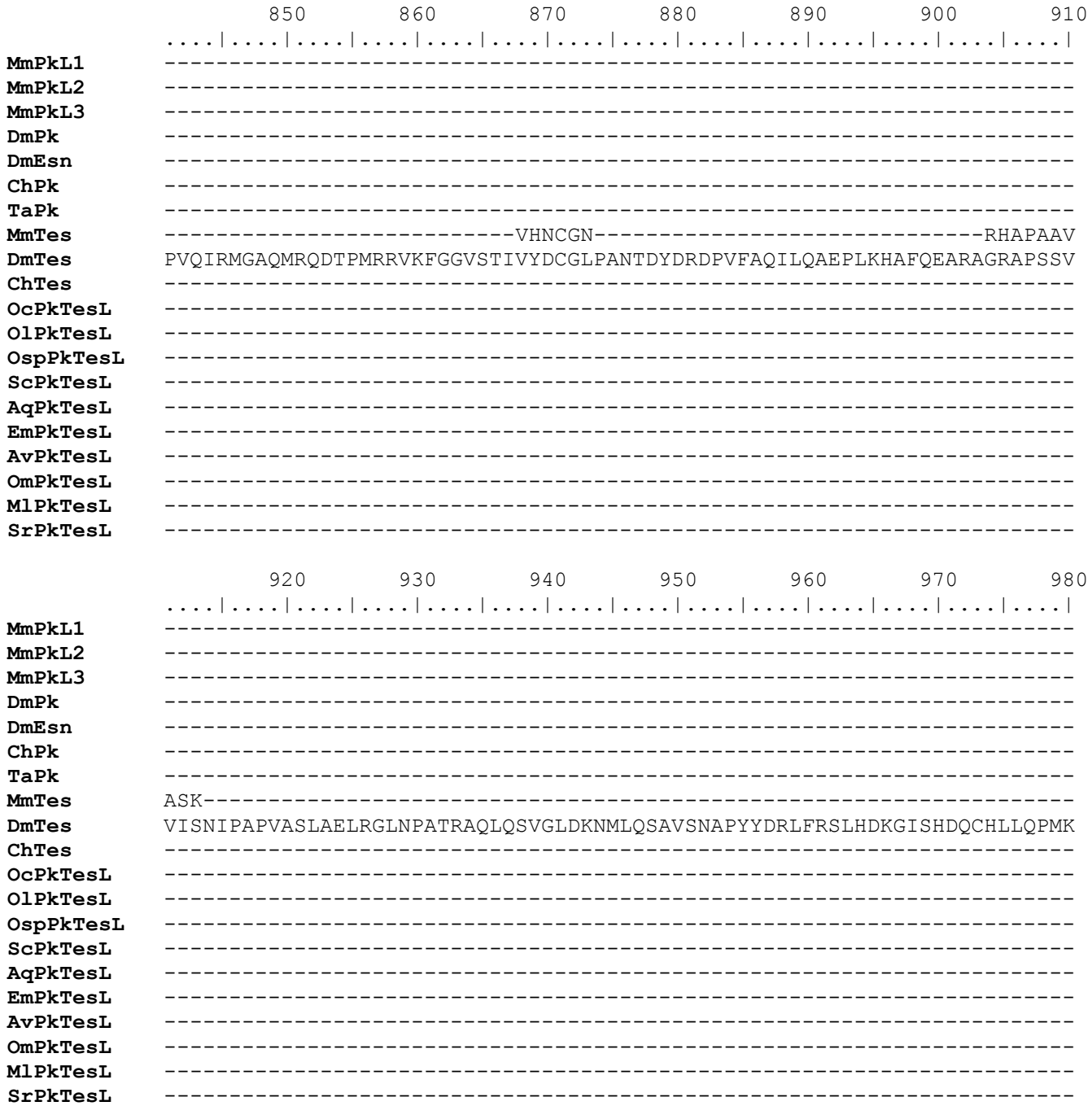
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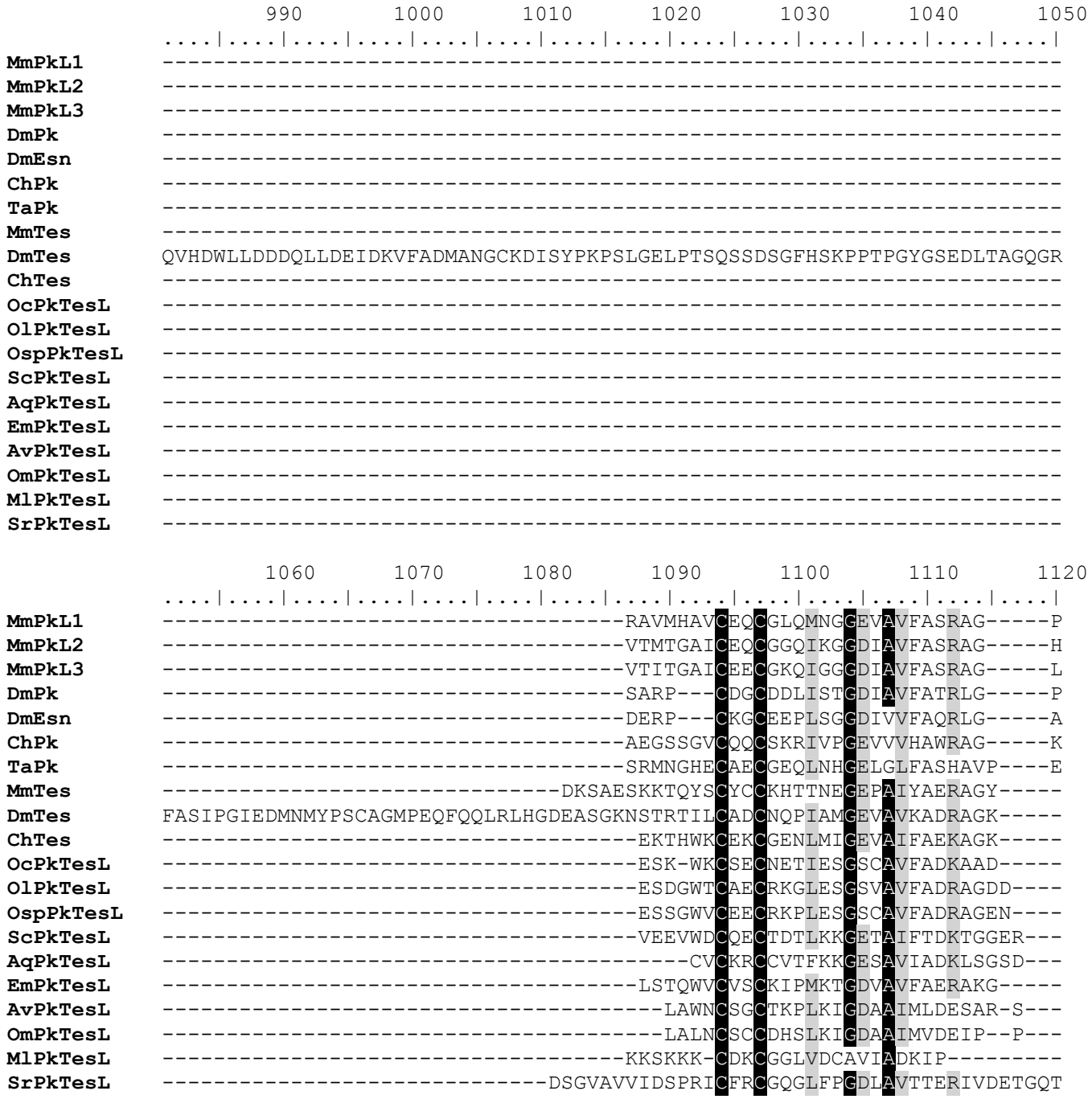
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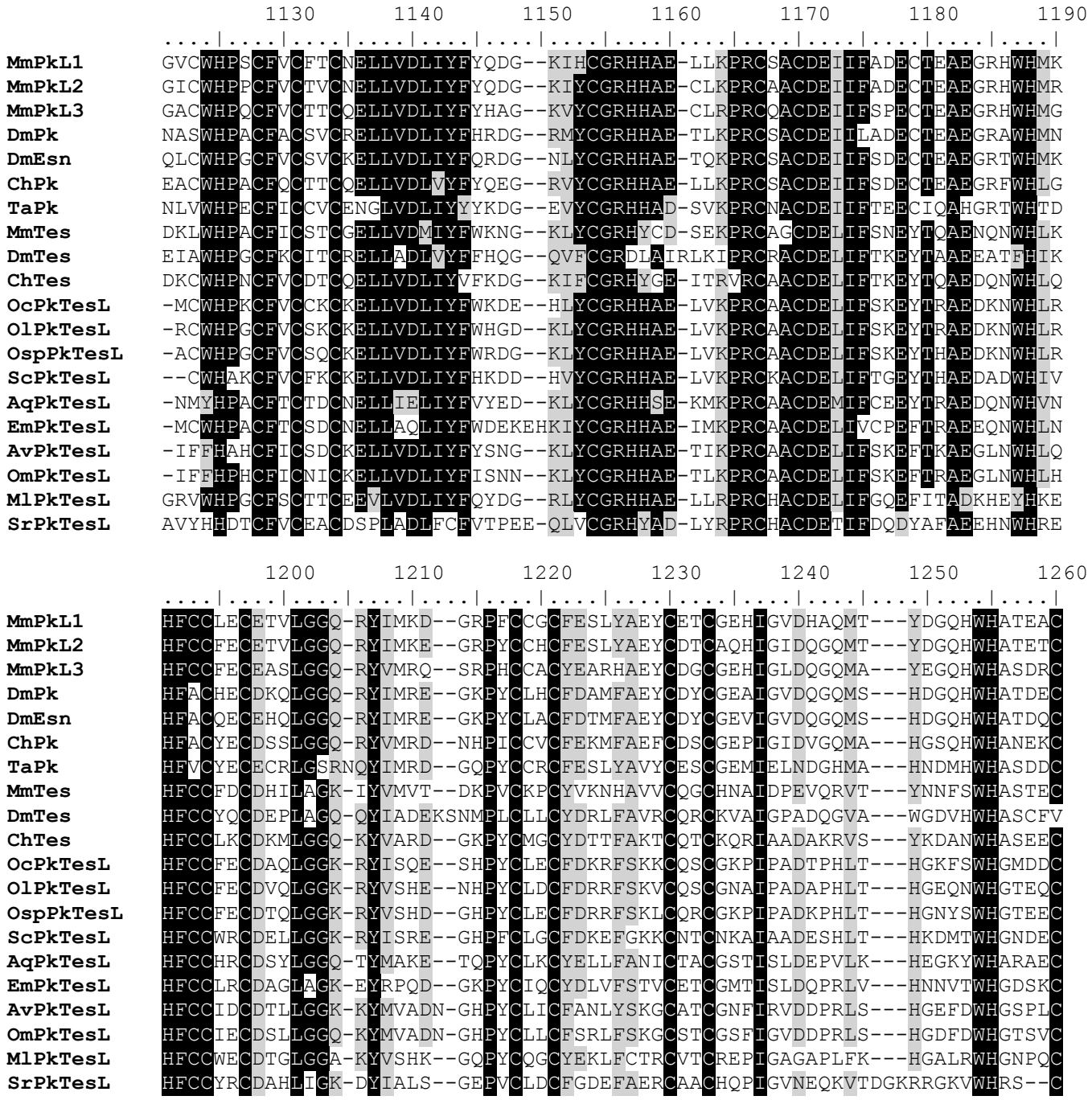
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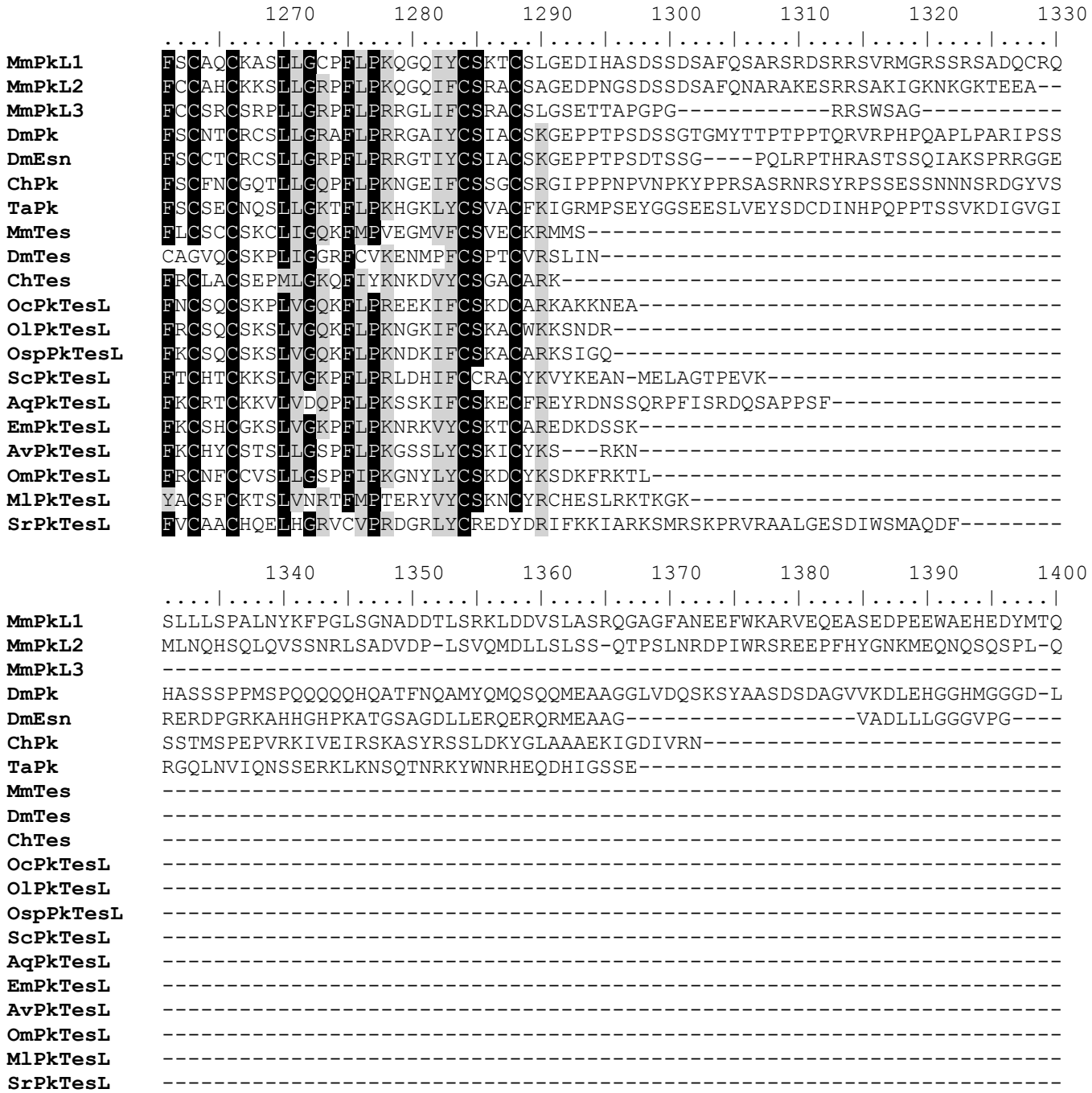
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OcPkTesL FNCSQCSKPLVGQKFLPREEKIFCSKDCARKAKKNEA----------
OlPkTesL FRCSQCSKSLVGQKFLPKNGKIFCSKACWKKSNDR----------
OspPkTesL FKCSQCSKSLVGQKFLPKNDKIFCSKACARKSIGQ----------
ScPkTesL FTCHTCKKSLVGKPFLPRLDHIFCCRACYKVYKEAN-MELAGTPEVK----------
AqPkTesL FKCRTCKKVLVDQPFLPKSSKIFCSKECFREYRDNSSQRPFISRDQSAPPSF----------
EmPkTesL FKCSHCGKSLVGKPFLPKNRKVYCSKTCAREDKDSSK----------
AvPkTesL FKCHYCSTSLLGSPFLPKGSSLYCSKICYKS---RKN----------
OmPkTesL FRCNFCCVSLLGSPFIPKGNYLYCSKDCYKSDKFRKTL----------
MlPkTesL YACSFCKTSLVNRTFMPTERYVYCSKNCYRCHESLRKTKGK----------
SrPkTesL FVCAACHQELHGRVCVPRDGRLYCREDYDRIFKKIARKSMRSKPRVRAALGESDIWSMAQDF--------
1340 1350 1360 1370 1380 1390 1400
MmPkL1 SLLLSPALNYKFPGLSGNADDTLSRKLDDVSLASRQGAGFANEEFWKARVEQEASEDPEEWAEHEDYMTQ
MmPkL2 MLNQHSQLQVSSNRLSADVDP-LSVQMDLLSLSS-QTPSLNRDPIWRSREEPFHYGNKMEQNQSQSPL-Q
MmPkL3 ----------
DmPk HASSSPPMSPQQQQQHQATFNQAMYQMQSQQMEAAGGLVDQSKSYAASDSDAGVVKDLEHGGHMGGGD-L
DmEsn RERDPGRKAHHGHPKATGSAGDLLERQERQRMEAAG----------VADLLLGGGVPG----
ChPk SSTMSPEPVRKIVEIRSKASYRSSLDKYGLAAAEKIGDIVRN----------
TaPk RGQLNVIQNSSERKLKNSQTNRKYWNRHEQDHIGSSE----------
MmTes ----------
DmTes ----------
ChTes ----------
OcPkTesL ----------
OlPkTesL ----------
OspPkTesL ----------
ScPkTesL ----------
AqPkTesL ----------
EmPkTesL ----------
AvPkTesL ----------
OmPkTesL ----------
MlPkTesL ----------
SrPkTesL ----------

```
                1410      1420      1430      1440      1450      1460      1470
           ....|....|....|....|....|....|....|....|....|....|....|....|....|
MmPkL1     LLLKFGDKNLFQQ--QSSEVDPRASEHWIPDNMVTNKPEVKPN----HQGLASKKYQSDMYWAQSQDGLG
MmPkL2     LLSQCNIRTSYSPGGQGAGAQPDMWAKHFSNPKRSSSMALKGHGGSFIQECREDYYPGRLMSQESYSDMS
MmPkL3     ----------------------------TVTTPLTTS-----------------------------------
DmPk       TDFSGGRASSTSQNLSPLNSPGDFQPHFLPKPMELQRDGV----------------------------YN
DmEsn      ----------------------------MPRPAHPPP-------------------------------ID
ChPk       ----------------------------MPNGGVIKEESD---------------------------EK
TaPk       ------------------------------------------------------------------VIP
MmTes      ------------------------------------------------------------------
DmTes      ------------------------------------------------------------------
ChTes      ------------------------------------------------------------------
OcPkTesL   ------------------------------------------------------------------
OlPkTesL   ------------------------------------------------------------------
OspPkTesL  ------------------------------------------------------------------
ScPkTesL   ------------------------------------------------------------------
AqPkTesL   ------------------------------------------------------------------
EmPkTesL   ------------------------------------------------------------------
AvPkTesL   ------------------------------------------------------------------
OmPkTesL   ------------------------------------------------------------------
MlPkTesL   ------------------------------------------------------------------
SrPkTesL   ------------------------------------------------------------------

                1480      1490      1500      1510      1520      1530      1540
           ....|....|....|....|....|....|....|....|....|....|....|....|....|
MmPkL1     DSAYGSHPGPASSRRLQELDLD-HGAAGYTHDQSQWYEDSLECLSDLKP-EQSIRDSMDSLALSNITGAS
MmPkL2     SQSFNETRGSIPVPKYEEEEEEEEGGISTQQCRPRRPLSSLKYTEDMTPTEQTPRGSMESLALSNATGLS
MmPkL3     TASFSATEG-----------------------------------------------TSETASKGTCTK
DmPk       FNEMSSNLDAAWSAKPTNSYHLQRQLLENPHTASMPELAGKLVAPPAHMQHLSQLHAVSSHQFQQHEYAD
DmEsn      LTELGISLDNICAGD--KSIFGDTQTLTN----SMPDML--------------LSKADDSHSYQSIDKIN
ChPk       DETSSTCSSVASSRAKELPSFPPSNRHSKKPILRVPPKQRPKPTGPEIWIDMVPPKEATTHRKQEEDWEK
TaPk       ESFTGASSGLAYSRS-----------------------------------------QKLNSYRSRDNNAEF
MmTes      ------------------------------------------------------------------
DmTes      ------------------------------------------------------------------
ChTes      ------------------------------------------------------------------
OcPkTesL   ------------------------------------------------------------------
OlPkTesL   ------------------------------------------------------------------
OspPkTesL  ------------------------------------------------------------------
ScPkTesL   ------------------------------------------------------------------
AqPkTesL   ------------------------------------------------------------------
EmPkTesL   ------------------------------------------------------------------
AvPkTesL   ------------------------------------------------------------------
OmPkTesL   ------------------------------------------------------------------
MlPkTesL   ------------------------------------------------------------------
SrPkTesL   ------------------------------------------------------------------
```

```
                1550      1560      1570      1580      1590      1600      1610
           ....|....|....|....|....|....|....|....|....|....|....|....|....|....|
MmPkL1     VDGESKPR--PSLYSLQNFEEIEAEDC-EKMSNMGTLNSSMLHRSAESLQSLNSGLCPEKILPEEKPAHL
MmPkL2     AEGGAKRQEHLSRFSMPDLSKDSGMNVSEKLSNMGTLNSSMQFRSAESVRSLLSAQQYQEMEGNLHQLSN
MmPkL3     AEPAAGPE----------------------------EPSHFLRGAPHRHSMPELGLRSAPEPPTESPGH
DmPk       ILHPPPPP--PGEIPELPTPNLSVASTALPPELMGSPTHSAGDRSLNTPMSTQSASHAPPHPVSILSGAS
DmEsn      LNSPS-------------NSDLTQSTQELANELELD-NEPVRELPHDGYEQLFANNRNQEHPAEQYD---
ChPk       QSVRSMRS------------NRSTTSTKKYGDAMSHLNGNDTIERLVQGERQINRRHRRRKVDDSYFSDY
TaPk       SKNNSNIR----------------------------RSRSRSNGHDSAQSNPNNQIEVETASANDHYNY
MmTes      ------------------------------------------------------------------------
DmTes      ------------------------------------------------------------------------
ChTes      ------------------------------------------------------------------------
OcPkTesL   ------------------------------------------------------------------------
OlPkTesL   ------------------------------------------------------------------------
OspPkTesL  ------------------------------------------------------------------------
ScPkTesL   ------------------------------------------------------------------------
AqPkTesL   ------------------------------------------------------------------------
EmPkTesL   ------------------------------------------------------------------------
AvPkTesL   ------------------------------------------------------------------------
OmPkTesL   ------------------------------------------------------------------------
MlPkTesL   ------------------------------------------------------------------------
SrPkTesL   ------------------------------------------------------------------------

                1620      1630      1640      1650      1660      1670      1680
           ....|....|....|....|....|....|....|....|....|....|....|....|....|....|
MmPkL1     PV-LRRSKSQSRPQQ--VKFSDDVIDNGSYDIE-IRQPPMSERTRRRAYHFEERGSRPHHHRHRRSRKSR
MmPkL2     PLGYRDLQSHGRMHQS-FDFDGGIASSKLPGQEGVHIQPMSERTRRRTTSRDD-NRRFRPHRSRRSRRSR
MmPkL3     PAPHPDDNAFGRQSTPRVSFRDPLVSEGGPRRT-LSAPPAQRRRPRSPPPRTPSCHHHHHHRRRRQRHRR
DmPk       SSSPMSGEPAKKKGVRFEGIPDTLPRSRSYSGNGAGTSGGGERERDRDKDKEGGGRHGHGHSSRRRRRRK
DmEsn      -DEQLDNRPMK--EVRFHSVQDTMSRSKSYTDNSNARR------------------------RRRRRNQ
ChPk       EVERRKRTQRRKQTPLVYQMDDEKPNIPLMTVKSRSTESLDAGKARVAGRRDE----------RDGKKKR
TaPk       NNPTKNPQHRKSPKQKKYTKNETMALEGPSSELKFKKYSSIDRIGEGIAYAQP----------LDRIRE
MmTes      ------------------------------------------------------------------------
DmTes      ------------------------------------------------------------------------
ChTes      ------------------------------------------------------------------------
OcPkTesL   ------------------------------------------------------------------------
OlPkTesL   ------------------------------------------------------------------------
OspPkTesL  ------------------------------------------------------------------------
ScPkTesL   ------------------------------------------------------------------------
AqPkTesL   ------------------------------------------------------------------------
EmPkTesL   ------------------------------------------------------------------------
AvPkTesL   ------------------------------------------------------------------------
OmPkTesL   ------------------------------------------------------------------------
MlPkTesL   ------------------------------------------------------------------------
SrPkTesL   ------------------------------------------------------------------------
```

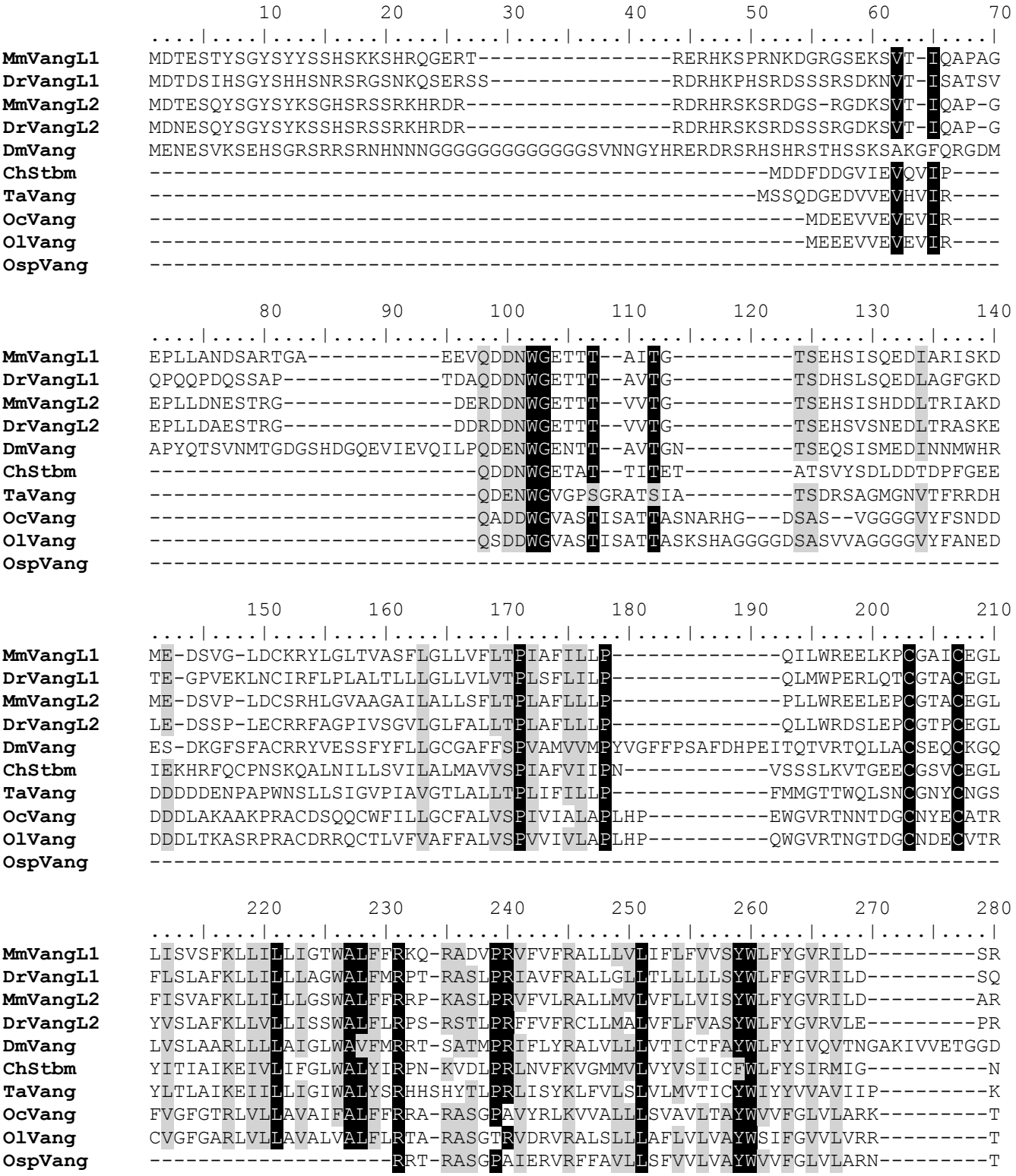
```
                1690      1700      1710      1720      1730      1740      1750
           ....|....|....|....|....|....|....|....|....|....|....|....|....|....|
MmPkL1     SDNALNLVTERKYSA--KDRLRLYTPDNYEKFIQNKSARELQAYMQNANLYSQYAHATSDYALQNPGMNR
MmPkL2     SDNALHLASEREVIARLKERPPLRAREDYDQFMRQRSFQESLGQGSRRDLYSQCPRTVSDLALQNAFGER
MmPkL3     RG----------------------SHHHHHHPGRHGHHRCDLGSGSDSGSCSSSP---------------
DmPk       SSSSSSHHRSGSGHR----------SHSTTRADTYAPAQPLSSSYQGPPSVLQAANLVHESPSRQQRERE
DmEsn      SRSSSEMQINQTNLR----------LHN---AQTQVGTTPLNLLNN-----------------------
ChPk       TKSETNLTNSKNYKS---------KNDAVANLRLNIDVNSPKKQSYN----------------------
TaPk       ADQSILVAKGYKKSE-----------------------------------------------------
MmTes      -------------------------------------------------------------------
DmTes      -------------------------------------------------------------------
ChTes      -------------------------------------------------------------------
OcPkTesL   -------------------------------------------------------------------
OlPkTesL   -------------------------------------------------------------------
OspPkTesL  -------------------------------------------------------------------
ScPkTesL   -------------------------------------------------------------------
AqPkTesL   -------------------------------------------------------------------
EmPkTesL   -------------------------------------------------------------------
AvPkTesL   -------------------------------------------------------------------
OmPkTesL   -------------------------------------------------------------------
MlPkTesL   -------------------------------------------------------------------
SrPkTesL   -------------------------------------------------------------------

                1760      1770      1780      1790      1800      1810      1820
           ....|....|....|....|....|....|....|....|....|....|....|....|....|....|
MmPkL1     FLGLCGEDDDSWCSSSTSSSDSEEEGYFLGQPIPQPRPQRFTYYTDDLSSPAS-ALPTPQFTQRTT----
MmPkL2     WGPYFTEYD--WCSTCSSSSESDNEGYFLGEPIPQPARLRYVTSDELLHKYSSYGVPKSSTLGGRG----
MmPkL3     --------------SSPSSESSEDDGFFLGERIPLPPHLCRPRTTQDTSTETFNSPAQP--LVQES----
DmPk       RERERREESEESDVCSTCSSSSSSSEDYMMMYQLPQRRHYGGVRVSYVPNDALAYDRKRKPSE--------
DmEsn      ----LDNCDVASICSTCSSSSSSDMD-DYVYRLPARKHYGGVRVAYVPNDALAYERKKKMAQDSSLAPGA
ChPk       ------KMELSKKATNKKTESNDSRKTARSFGMFSAEDQQMTRINYVTQDDMAMDHRRNSKSPKKS----
TaPk       -------------CITGSSSDDSQPDTNVTFNLVGKLDIQRGKSPQKVSTANSFNESRKEKKVRIVD---
MmTes      -------------------------------------------------------------------
DmTes      -------------------------------------------------------------------
ChTes      -------------------------------------------------------------------
OcPkTesL   -------------------------------------------------------------------
OlPkTesL   -------------------------------------------------------------------
OspPkTesL  -------------------------------------------------------------------
ScPkTesL   -------------------------------------------------------------------
AqPkTesL   -------------------------------------------------------------------
EmPkTesL   -------------------------------------------------------------------
AvPkTesL   -------------------------------------------------------------------
OmPkTesL   -------------------------------------------------------------------
MlPkTesL   -------------------------------------------------------------------
SrPkTesL   -------------------------------------------------------------------
```

```
                  1830      1840
            ....|....|....|....|.
MmPkL1      -----KSKKKKGHKGKNCIIS
MmPkL2      -----QLHSRKRQKSKNCIIS
MmPkL3      -----HPVMPRQTRDKNCIVA
DmPk        ----LGGD-----KDKNCIIS
DmEsn       GNASVGGAPAIMHESKNCTIS
ChPk        --------KRKSKNQGQCVIS
TaPk        ----------EAVDKSKCIVM
MmTes       ----------------------
DmTes       ----------------------
ChTes       ----------------------
OcPkTesL    ----------------------
OlPkTesL    ----------------------
OspPkTesL   ----------------------
ScPkTesL    ----------------------
AqPkTesL    ----------------------
EmPkTesL    ----------------------
AvPkTesL    ----------------------
OmPkTesL    ----------------------
MlPkTesL    ----------------------
SrPkTesL    ----------------------
```

Abbreviations. Vertebrate: Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Cnidaria: Ch, *Clytia hemisphaerica.* Placozoa: Ta, *Trichoplax adhaerens*. Porifera: Aq, *Amphimedon queenslandica*; Av, *Aphrocalistes vastus*; Em, *Ephydatia muelleri*; *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; *Om, Oopsacas minuta*; *Osp, Oscarella sp*.; Sc, *Sycon ciliatum*. Ctenophora: Ml, *Mnemiopsis leidyi*. Choanoflagellata: Sr, *Salpingoeca rosetta*.

Figure S2.6: Strabismus/Van Gogh alignment. Threshold for shading has been fixed at 80% for both identity (black) and similarity (grey). The red square indicate the final PDZ binding motif.



Abbreviations. Vertebrate: Dr, *Danio rerio* and Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Cnidaria: Ch, *Clytia hemisphaerica.* Placozoa: Ta, *Trichoplax adhaerens*. Porifera: *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; *Om, Oopsacas minuta*; *Osp, Oscarella sp*.

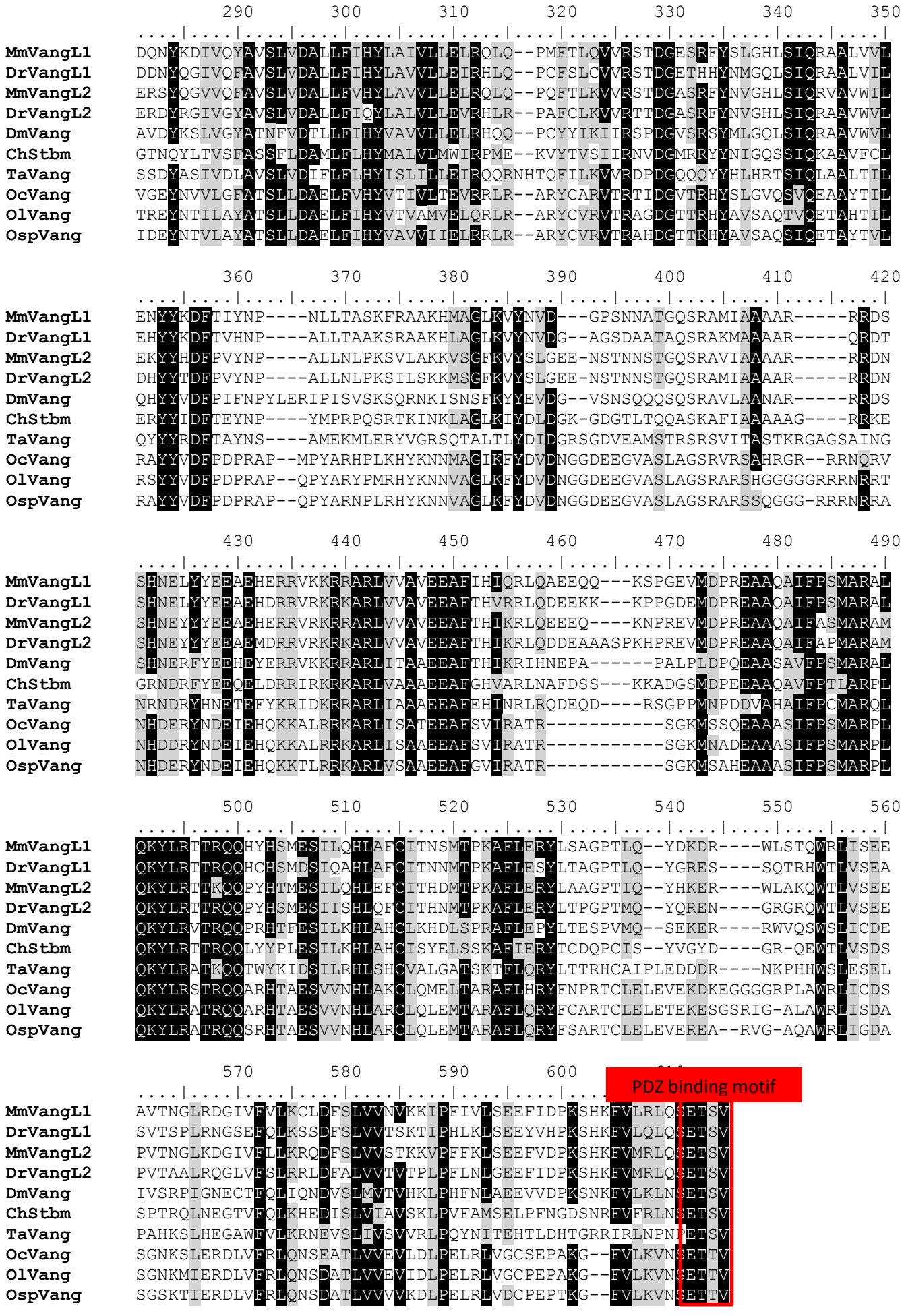
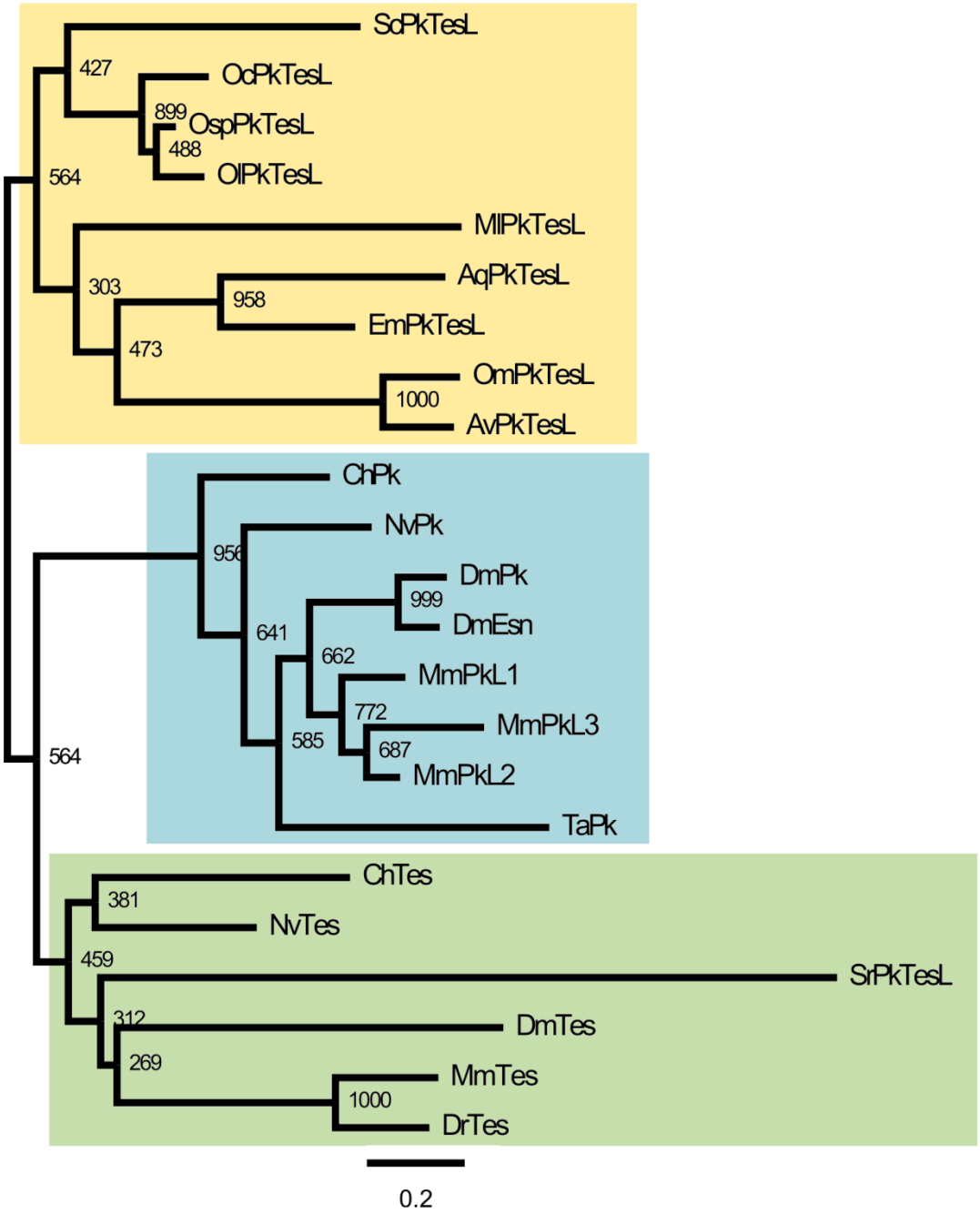
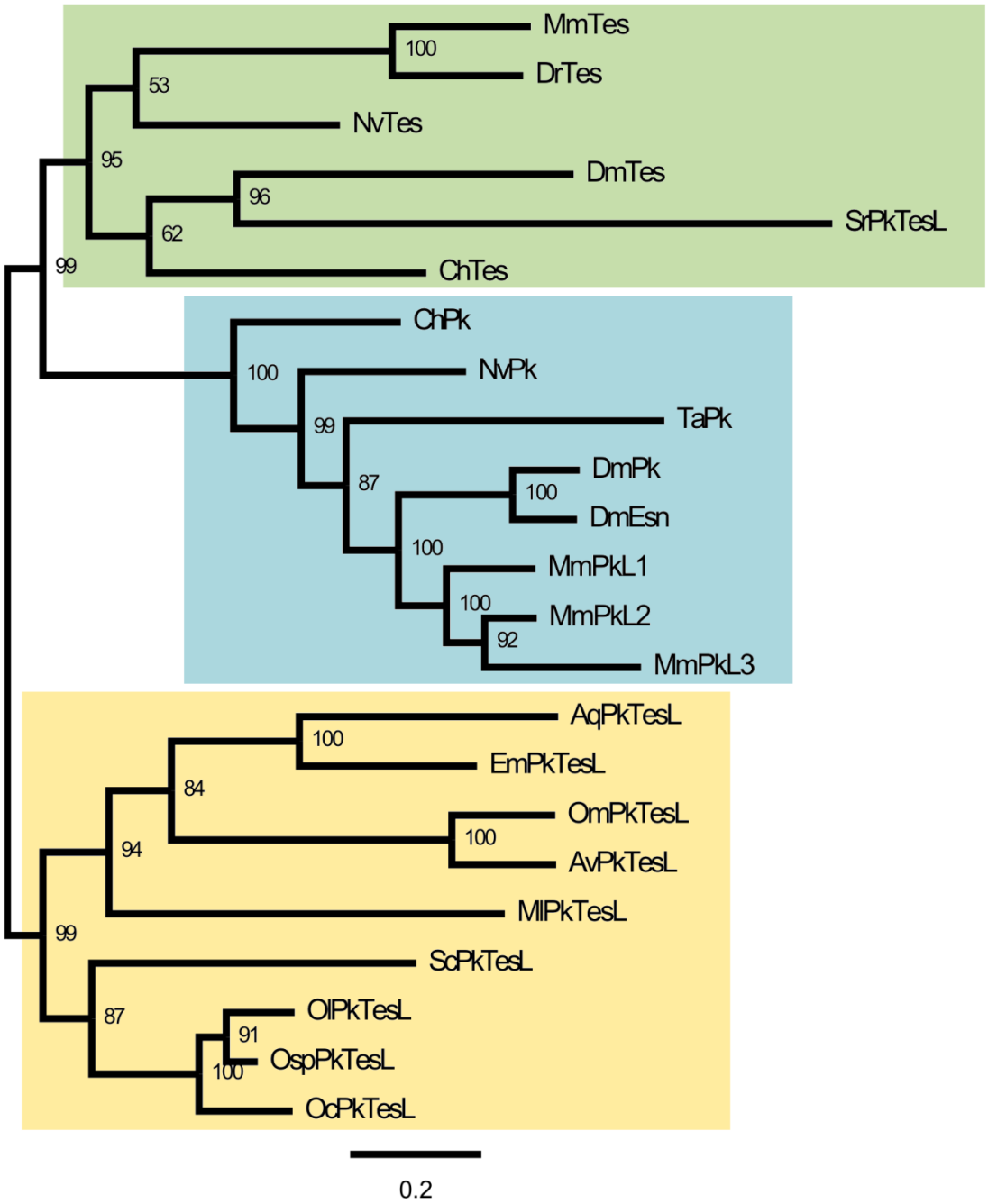

290 300 310 320 330 340 350
MmVangL1 DQNYKDIVQYAVSLVDALLFIHYLAIVLLELRQLQ--PMFTLQVVRSTDGESRFYSLGHLSIQRAALVVL
DrVangL1 DDNYQGIVQFAVSLVDALLFIHYLAVVLLEIRHLQ--PCFSLCVVRSTDGETHHYNMGQLSIQRAALVIL
MmVangL2 ERSYQGVVQFAVSLVDALLFVHYLAVVLLELRQLQ--PQFTLKVVRSTDGASRFYNVGHLSIQRVAVWIL
DrVangL2 ERDYRGIVGYAVSLVDALLFIQYLALVLLEVRHLR--PAFCLKVVRTTDGASRFYNVGHLSIQRAAVWVL
DmVang AVDYKSLVGYATNFVDTLLFIHYVAVVLLELRHQQ--PCYYIKIIRSPDGVSRSYMLGQLSIQRAAVWVL
ChStbm GTNQYLTVSFASSFLDAMLFLHYMALVLMWIRPME--KVYTVSIIRNVDGMRRYYNIGQSSIQKAAVFCL
TaVang SSDYASIVDLAVSLVDIFLFLHYISLILLEIRQQRNHTQFILKVVRDPDGQQQYYHLHRTSIQLAALTIL
OcVang VGEYNVVLGFATSLLDAELFVHYVTIVLTEVRRLR--ARYCARVTRTIDGVTRHYSLGVQSVQEAAYTIL
OlVang TREYNTILAYATSLLDAELFIHYVTVAMVELQRLR--ARYCVRVTRAGDGTTRHYAVSAQTVQETAHTIL
OspVang IDEYNTVLAYATSLLDAELFIHYVAVVIIELRRLR--ARYCVRVTRAHDGTTRHYAVSAQSIQETAYTVL
360 370 380 390 400 410 420
MmVangL1 ENYYKDFTIYNP----NLLTASKFRAAKHMAGLKVYNVD---GPSNNATGQSRAMIAAAAR-----RRDS
DrVangL1 EHYYKDFTVHNP----ALLTAAKSRAAKHLAGLKVYNVDG--AGSDAATAQSRAKMAAAAR-----QRDT
MmVangL2 EKYYHDFPVYNP----ALLNLPKSVLAKKVSGFKVYSLGEE-NSTNNSTGQSRAVIAAAAR-----RRDN
DrVangL2 DHYYTDFPVYNP----ALLNLPKSILSKKMSGFKVYSLGEE-NSTNNSTGQSRAMIAAAAR-----RRDN
DmVang QHYYVDFPIFNPYLERIPISVSKSQRNKISNSFKYYEVDG--VSNSQQQSQSRAVLAANAR-----RRDS
ChStbm ERYYIDFTEYNP----YMPRPQSRTKINKLAGLKIYDLDGK-GDGTLTQQASKAFIAAAAAG----RRKE
TaVang QYYYRDFTAYNS----AMEKMLERYVGRSQTALTLYDIDGRSGDVEAMSTRSRSVITASTKRGAGSAING
OcVang RAYYVDFPDPRAP--MPYARHPLKHYKNNMAGIKFYDVDNGGDEEGVASLAGSRVRSAHRGR--RRNQRV
OlVang RSYYVDFPDPRAP--QPYARYPMRHYKNNVAGLKFYDVDNGGDEEGVASLAGSRARSHGGGGGRRRNRRT
OspVang RAYYVDFPDPRAP--QPYARNPLRHYKNNVAGLKFYDVDNGGDEEGVASLAGSRARSSQGGG-RRRNRRA
430 440 450 460 470 480 490
MmVangL1 SHNELYYEEAEHERRVKKRRARLVVAVEEAFIHIQRLQAEEQQ---KSPGEVMDPREAAQAIFPSMARAL
DrVangL1 SHNELYYEEAEHDRRVRKRKARLVVAVEEAFTHVRRLQDEEKK---KPPGDEMDPREAAQAIFPSMARAL
MmVangL2 SHNEYYYEEAEHERRVRKRRARLVVAVEEAFTHIKRLQEEEQ----KNPREVMDPREAAQAIFASMARAM
DrVangL2 SHNEYYYEEAEMDRRVRKRKARLVVAVEEAFTHIKRLQDDEAAASPKHPREVMDPREAAQAIFAPMARAM
DmVang SHNERFYEEHEYERRVKKRRARLITAAEEAFTHIKRIHNEPA------PALPLDPQEAASAVFPSMARAL
ChStbm GRNDRFYEEQELDRRIRKRKARLVAAAEEAFGHVARLNAFDSS---KKADGSMDPEEAAQAVFPTLARPL
TaVang NRNDRYHNETEFYKRIDKRRARLIAAAEEAFEHINRLRQDEQD----RSGPPMNPDDVAHAIFPCMARQL
OcVang NHDERYNDEIEHQKKALRRKARLISATEEAFSVIRATR-----------SGKMSSQEAAASIFPSMARPL
OlVang NHDDRYNDEIEHQKKALRRKARLISAAEEAFSVIRATR-----------SGKMNADEAAASIFPSMARPL
OspVang NHDERYNDEIEHQKKTLRRKARLVSAAEEAFGVIRATR-----------SGKMSAHEAAASIFPSMARPL
500 510 520 530 540 550 560
MmVangL1 QKYLRTTRQQHYHSMESILQHLAFCITNSMTPKAFLERYLSAGPTLQ--YDKDR----WLSTQWRLISEE
DrVangL1 QKYLRTTRQQHCHSMDSIQAHLAFCITNNMTPKAFLESYLTAGPTLQ--YGRES----SQTRHWTLVSEA
MmVangL2 QKYLRTTKQQPYHTMESILQHLEFCITHDMTPKAFLERYLAAGPTIQ--YHKER----WLAKQWTLVSEE
DrVangL2 QKYLRTTRQQPYHSMESIISHLQFCITHNMTPKAFLERYLTPGPTMQ--YQREN----GRGRQWTLVSEE
DmVang QKYLRVTRQQPRHTFESILKHLAHCLKHDLSPRAFLEPYLTESPVMQ--SEKER----RWVQSWSLICDE
ChStbm QKYLRTTRQQLYYPLESILKHLAHCISYELSSKAFIERYTCDQPCIS--YVGYD----GR-QEWTLVSDS
TaVang QKYLRATKQQTWYKIDSILRHLSHCVALGATSKTFLQRYLTTRHCAIPLEDDDR----NKPHHWSLESEL
OcVang QKYLRSTRQQARHTAESVVNHLAKCLQMELTARAFLHRYFNPRTCLELEVEKDKEGGGGRPLAWRLICDS
OlVang QKYLRATRQQARHTAESVVNHLARCLQLEMTARAFLQRYFCARTCLELETEKESGSRIG-ALAWRLISDA
OspVang QKYLRATRQQSRHTAESVVNHLARCLQLEMTARAFLQRYFSARTCLELEVEREA--RVG-AQAWRLIGDA
570 580 590 600
PDZ binding motif
MmVangL1 AVTNGLRDGIVFVLKCLDFSLVVNVKKIPFIVLSEEFIDPKSHKFVLRLQSETSV
DrVangL1 SVTSPLRNGSEFQLKSSDFSLVVTSKTIPHLKLSEEYVHPKSHKFVLQLQSETSV
MmVangL2 PVTNGLKDGIVFLLKRQDFSLVVSTKKVPFFKLSEEFVDPKSHKFVMRLQSETSV
DrVangL2 PVTAALRQGLVFSLRRLDFALVVTVTPLPFLNLGEEFIDPKSHKFVMRLQSETSV
DmVang IVSRPIGNECTFQLIQNDVSLMVTVHKLPHFNLAEEVVDPKSNKFVLKLNSETSV
ChStbm SPTRQLNEGTVFQLKHEDISLVIAVSKLPVFAMSELPFNGDSNRFVFRLNSETSV
TaVang PAHKSLHEGAWFVLKRNEVSLIVSVVRLPQYNITEHTLDHTGRRIRLNPNPETSV
OcVang SGNKSLERDLVFRLQNSEATLVVEVLDLPELRLVGCSEPAKG--FVLKVNSETTV
OlVang SGNKMIERDLVFRLQNSDATLVVEVIDLPELRLVGCPEPAKG--FVLKVNSETTV
OspVang SGSKTIERDLVFRLQNSDATLVVVVKDLPELRLVDCPEPTKG--FVLKVNSETTV

Figure S2.7: Maximum likelihood unrooted tree of PET family.



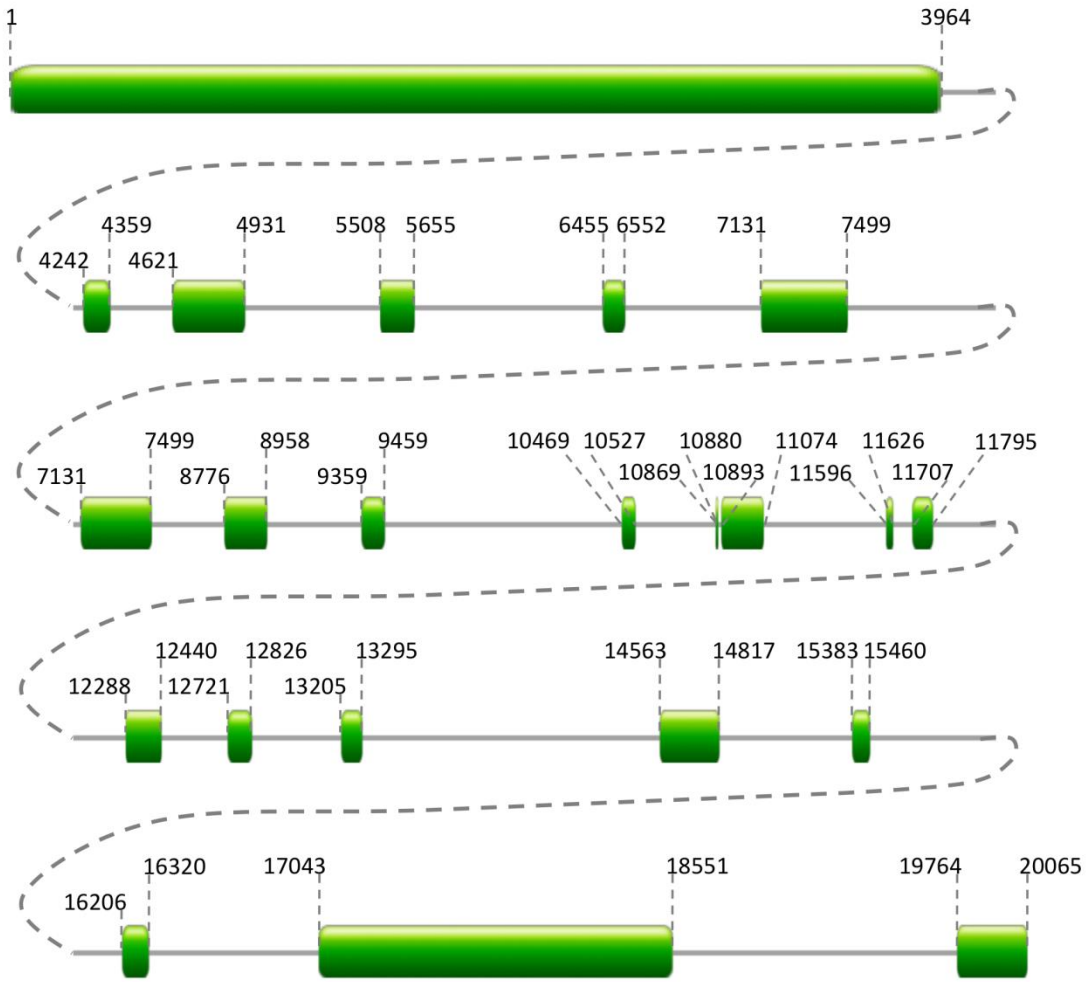
Percentage bootstrap support obtained in maximum likelihood analysis is indicated each node. Abbreviations. Vertebrate: Dr, *Danio rerio*; Gg, *Gallus gallus*; Hs, *Homo sapiens* and Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Mollusca: Ac, *Aplysia californica* and Cg, *Crassotrea gigantea*. Ambulacraria: Hp, *Hemicentrotus pulcherrimus*; Sk, *Saccoglossus kowalevskii* and Sp, *Strongylocentrotus purpuratus*. Cnidaria: Ch, *Clytia hemisphaerica;* Nv, *Nematostella vectensis.* Placozoa: Ta, *Trichoplax adhaerens*. Porifera: Aq, *Amphimedon queenslandica*; Av, *Aphrocalistes vastus*; Em, *Ephydatia muelleri*; *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; *Om, Oopsacas minuta*; *Osp, Oscarella sp.*; Sc, *Sycon ciliatum*. Ctenophora: Ml, *Mnemiopsis leidyi*. Choanoflagellata: Sr, *Salpingoeca rosetta*.

Figure S2.8: Bayesian unrooted tree of PET family.



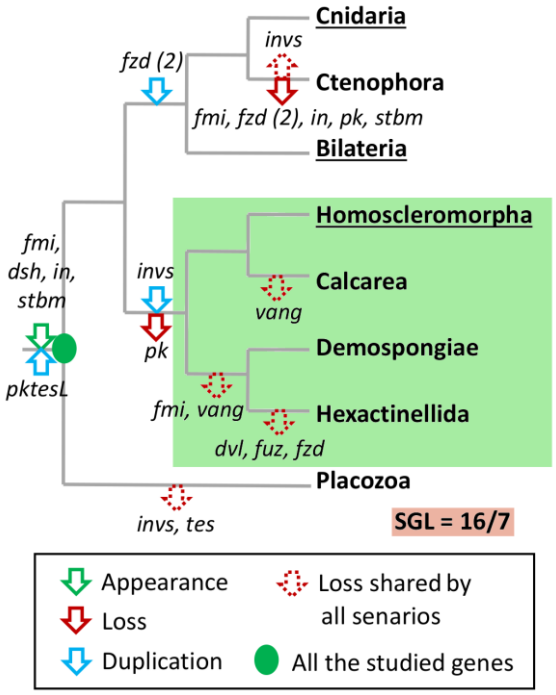
Posterior probability obtained in Bayesian analysis is indicated above each node. Abbreviations. Vertebrate: Dr, *Danio rerio*; Gg, *Gallus gallus*; Hs, *Homo sapiens* and Mm, *Mus musculus.* Hexapoda: Dm, *Drosophila melanogaster.* Mollusca: Ac, *Aplysia californica* and Cg, *Crassotrea gigantea*. Ambulacraria: Hp, *Hemicentrotus pulcherrimus*; Sk, *Saccoglossus kowalevskii* and Sp, *Strongylocentrotus purpuratus*. Cnidaria: Ch, *Clytia hemisphaerica;* Nv, *Nematostella vectensis.* Placozoa: Ta, *Trichoplax adhaerens*. Porifera: Aq, *Amphimedon queenslandica*; Av, *Aphrocalistes vastus*; Em, *Ephydatia muelleri*; *Oc, Oscarella carmela*; *Ol, Oscarella lobularis*; *Om, Oopsacas minuta*; *Osp, Oscarella sp.*; Sc, *Sycon ciliatum*. Ctenophora: Ml, *Mnemiopsis leidyi*. Choanoflagellata: Sr, *Salpingoeca rosetta*.

Figure S2.9: Intro/exon composition of *flamingo* in *Sycon ciliatum*.



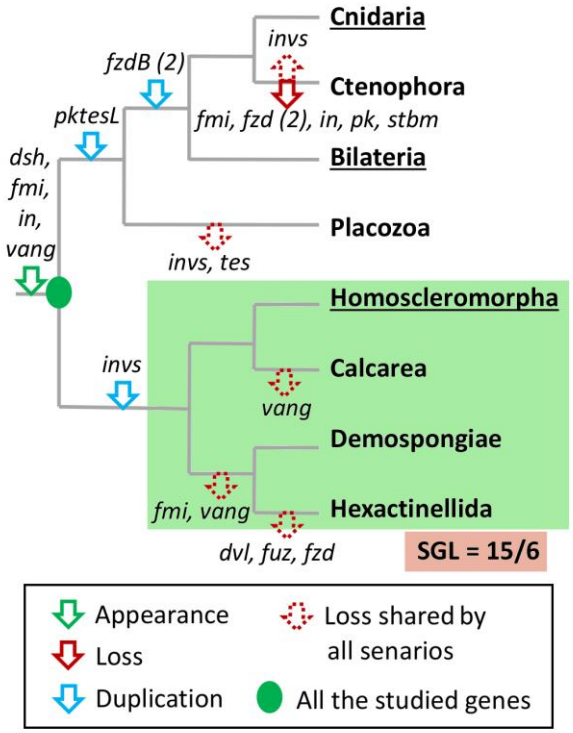
Location of exons is indicated in base pairs along the gene.

Figure S2.10: Alternative scenario 1 of the PCP players during animal evolution.



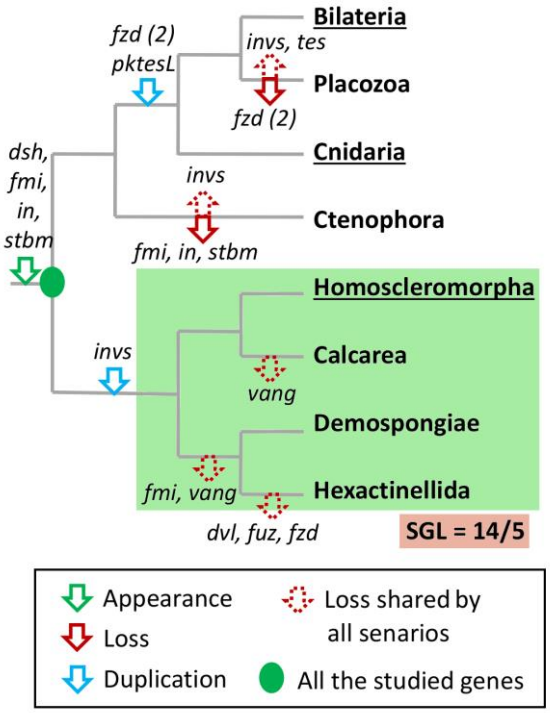
The emergence (green arrows), duplications (blue arrows) and secondarily losses (red arrows) of PCP genes are indicated (16 secondarily gene losses, SGL), based on genome analyses. Abbreviations. *dsh*, *dishevelled*; *fmi*, *flamingo*; *fuz*, *fuzzy*; *fzd*, *frizzled*; *intu*, *inturned*; *invs*, *inversin*; *pktesL*, *prickle-testin like*; *pk*, *prickle*; *tes*, *testin* and *vang*, *van gogh*.

Figure S2.11: Alternative scenario 2 of the PCP players during animal evolution.



The emergence (green arrows), duplications (blue arrows) and secondarily losses (red arrows) of PCP genes are indicated (15 secondarily gene losses, SGL), based on genome analyses. Abbreviations. *dsh*, *dishevelled*; *fmi*, *flamingo*; *fuz*, *fuzzy*; *fzd*, *frizzled*; *intu*, *inturned*; *invs*, *inversin*; *pktesL*, *prickle-testin like*; *pk*, *prickle*; *tes*, *testin* and *vang*, *van gogh*.

Figure S2.12: Alternative scenario 3 of the PCP players during animal evolution.



The emergence (green arrows), duplications (blue arrows) and secondarily losses (red arrows) of PCP genes are indicated (14 secondarily gene losses, SGL), based on genome analyses. Abbreviations. *dsh*, *dishevelled*; *fmi*, *flamingo*; *fuz*, *fuzzy*; *fzd*, *frizzled*; *intu*, *inturned*; *invs*, *inversin*; *pktesL*, *prickle-testin like*; *pk*, *prickle*; *tes*, *testin* and *vang*, *van gogh*.