



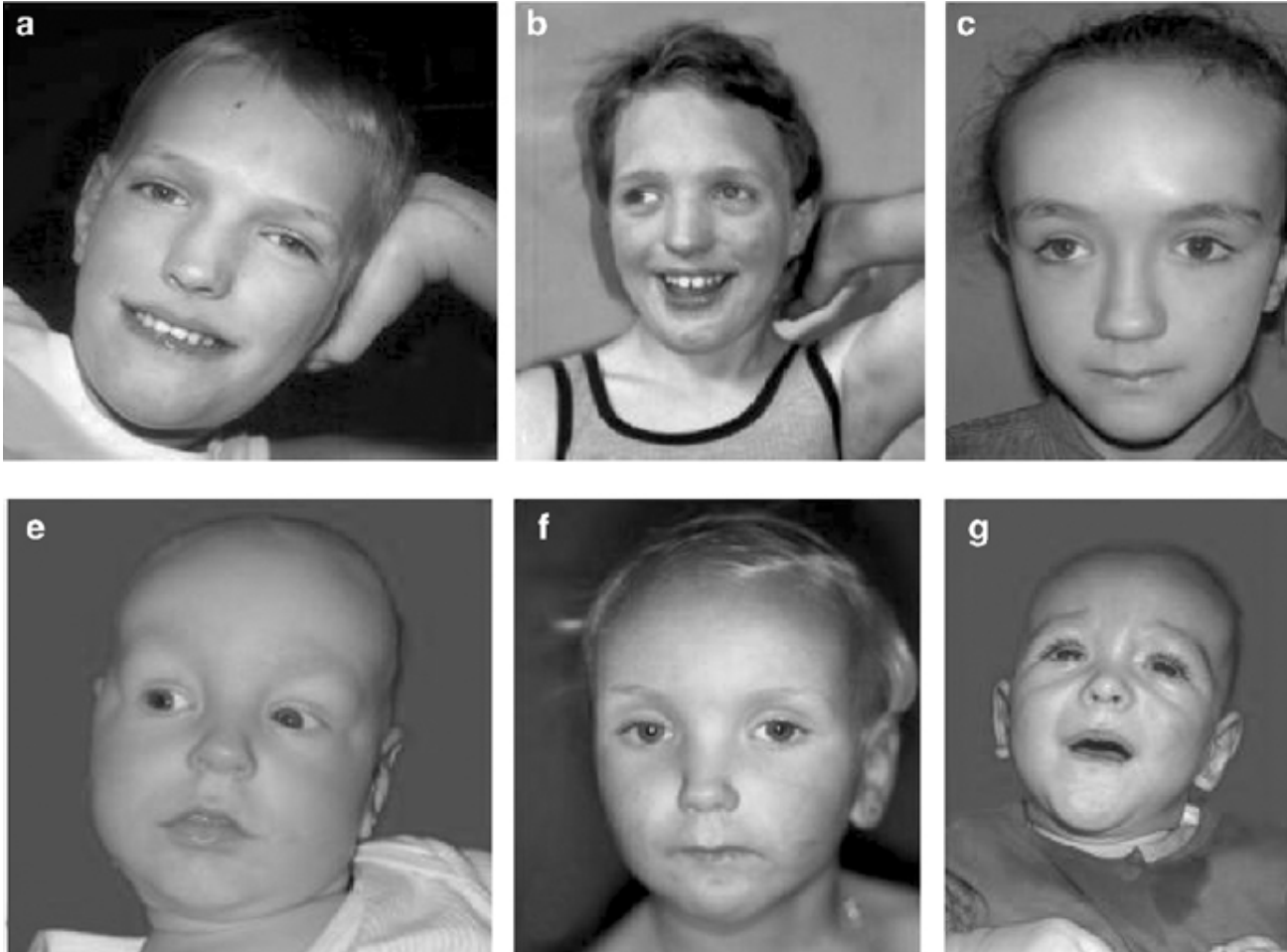
Sotos syndrome and the *NSD1* gene



Jamie Masliah
Genetics 564

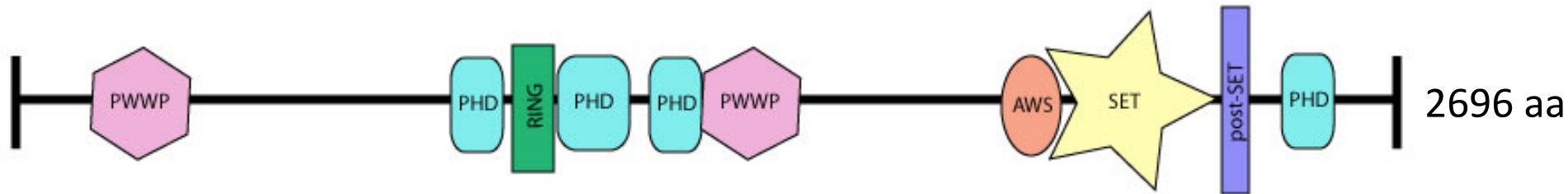


What is Sotos syndrome?



Impaired Learning

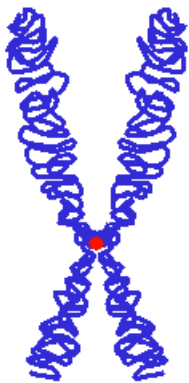
NSD1 is mutated in Sotos syndrome



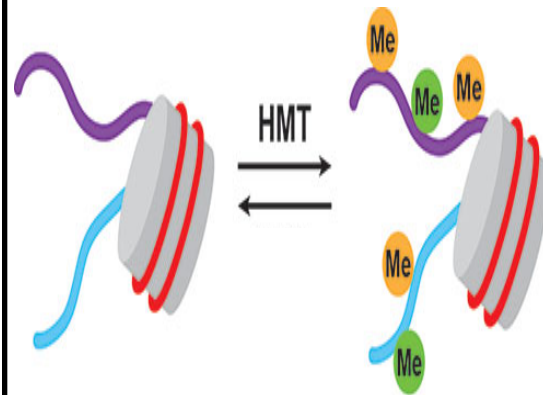
GO TERMS

Molecular Function

Zn²⁺



Biological Process



Cellular Component

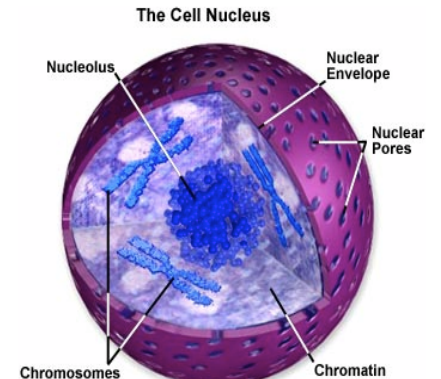
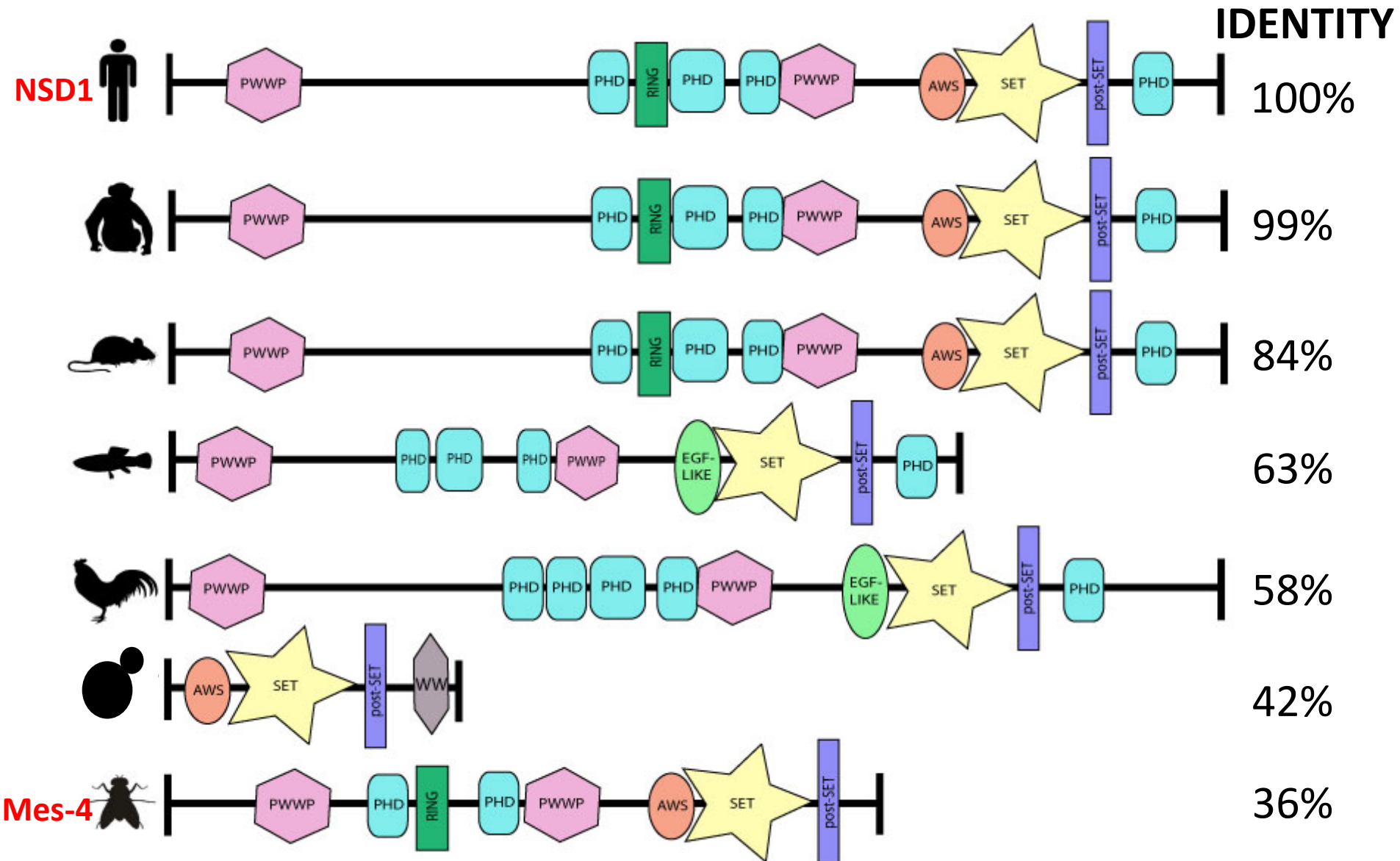
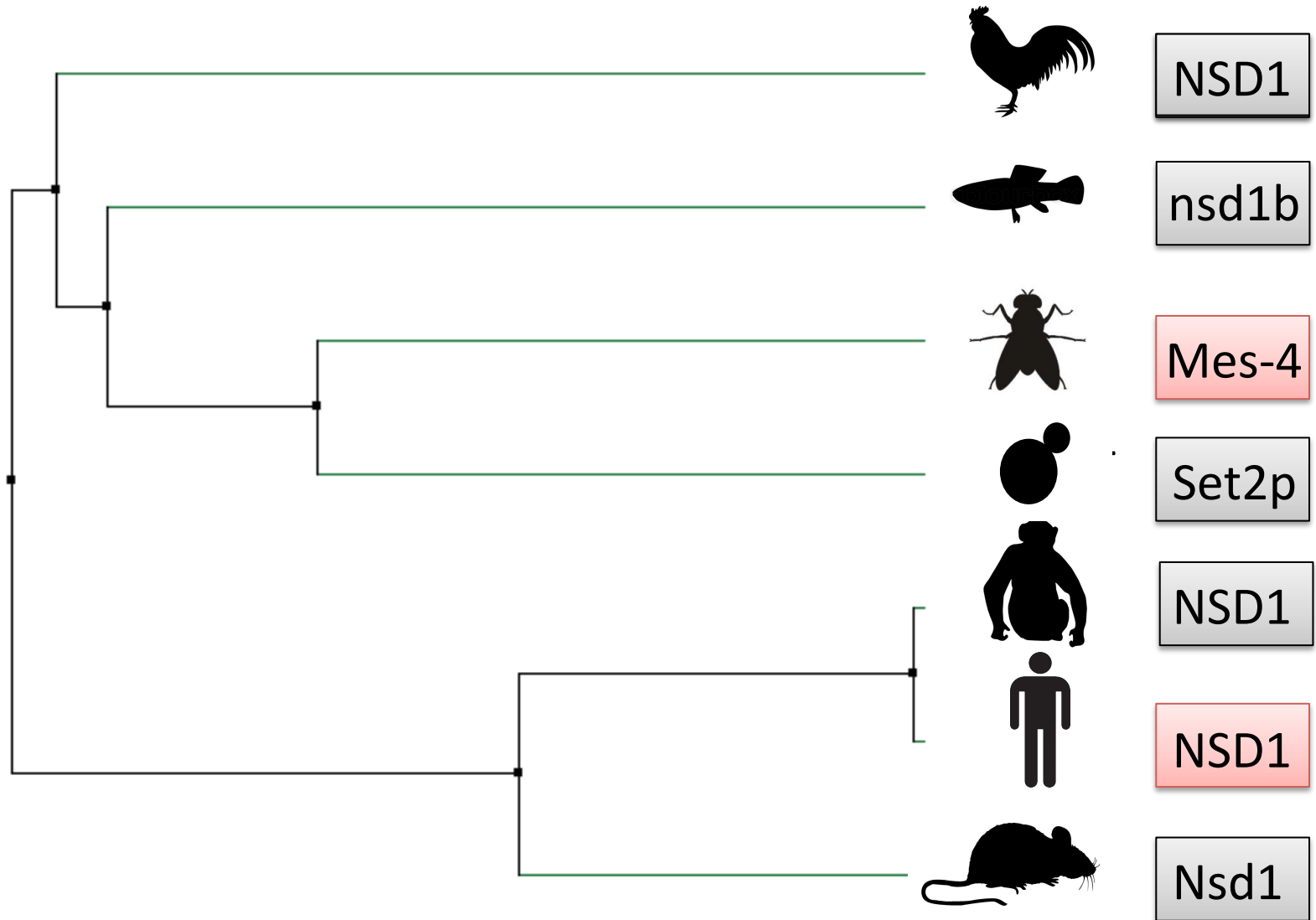


Figure 1

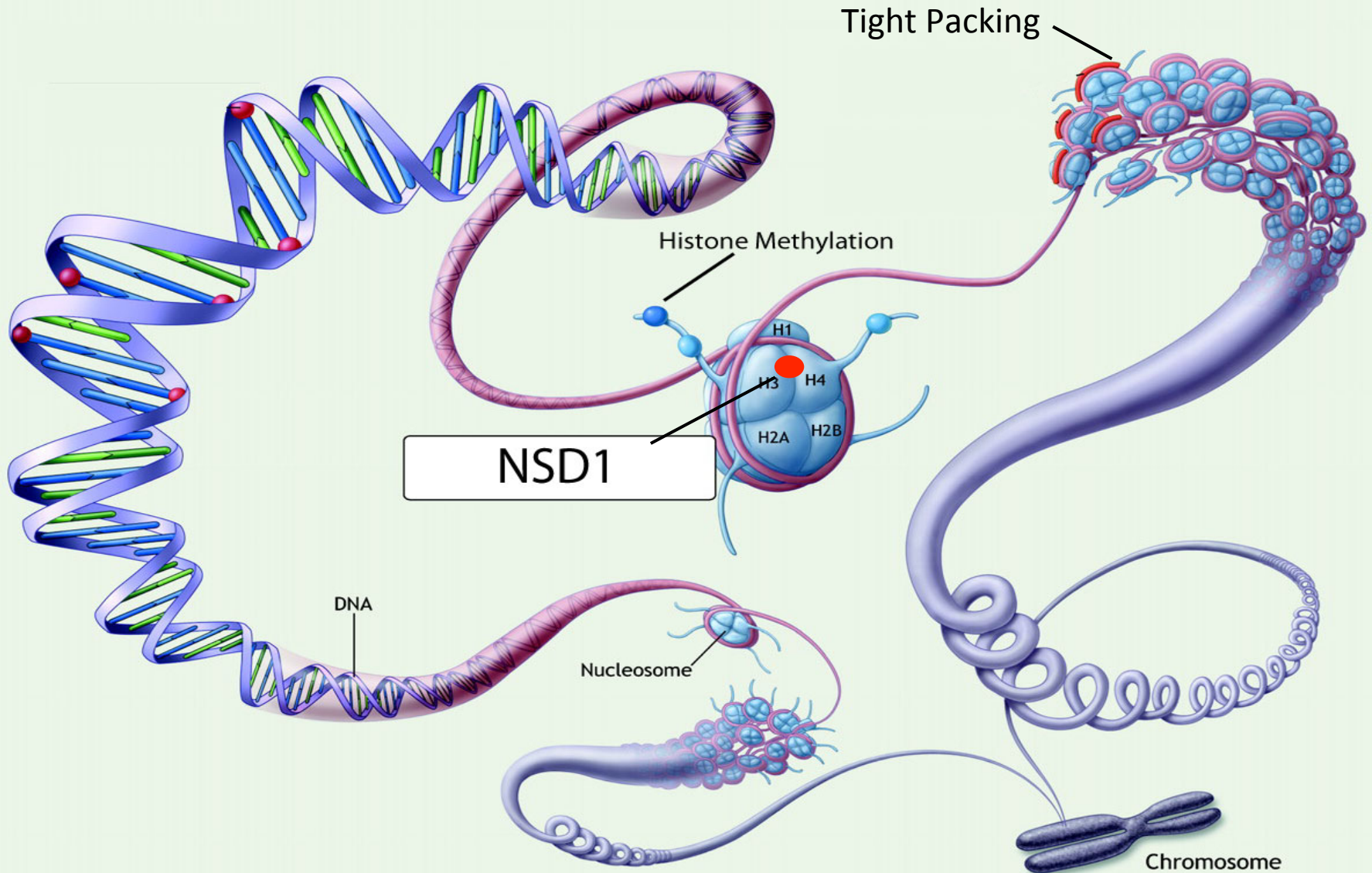
How highly conserved is **NSD1**?



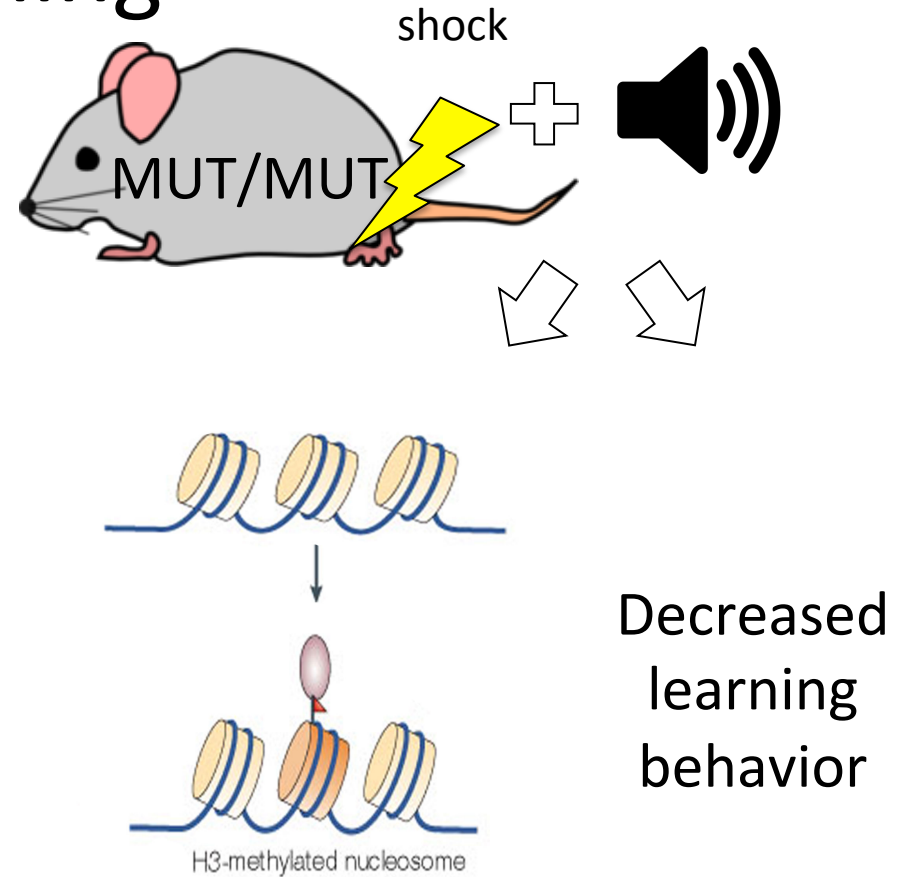
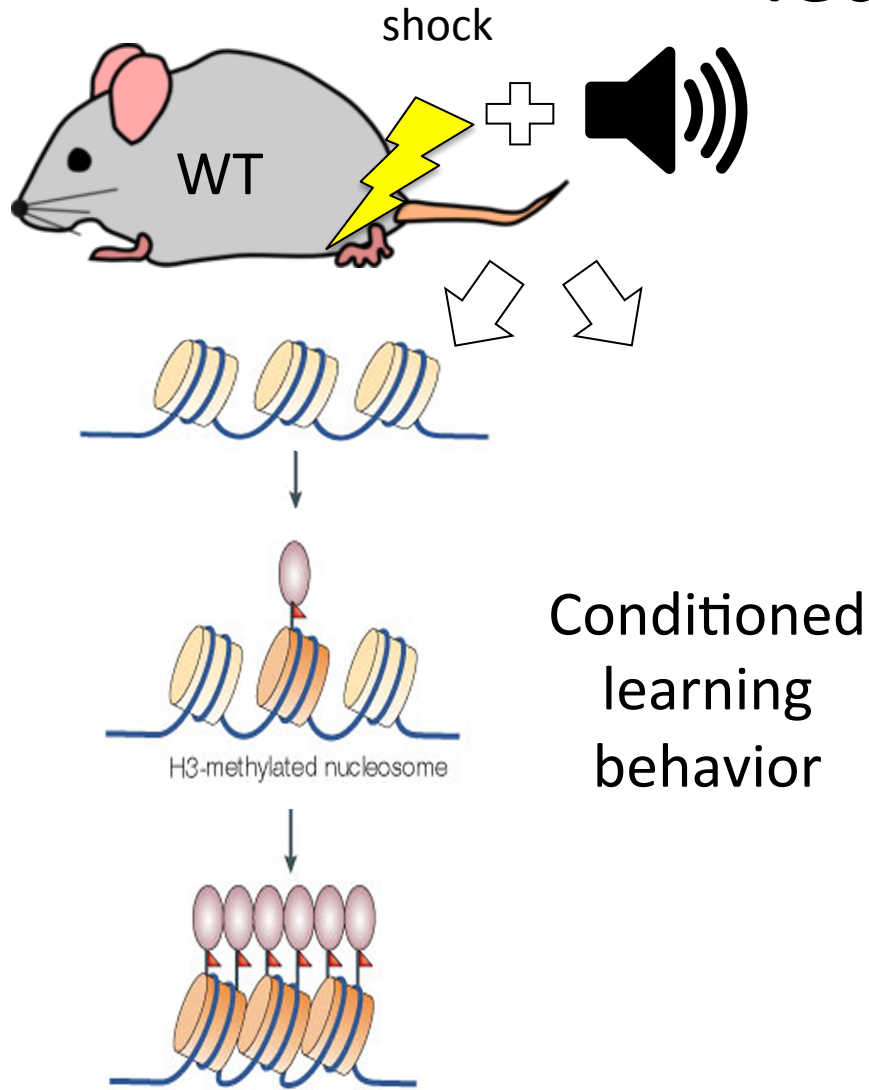
How similar are the NSD1 homologs?



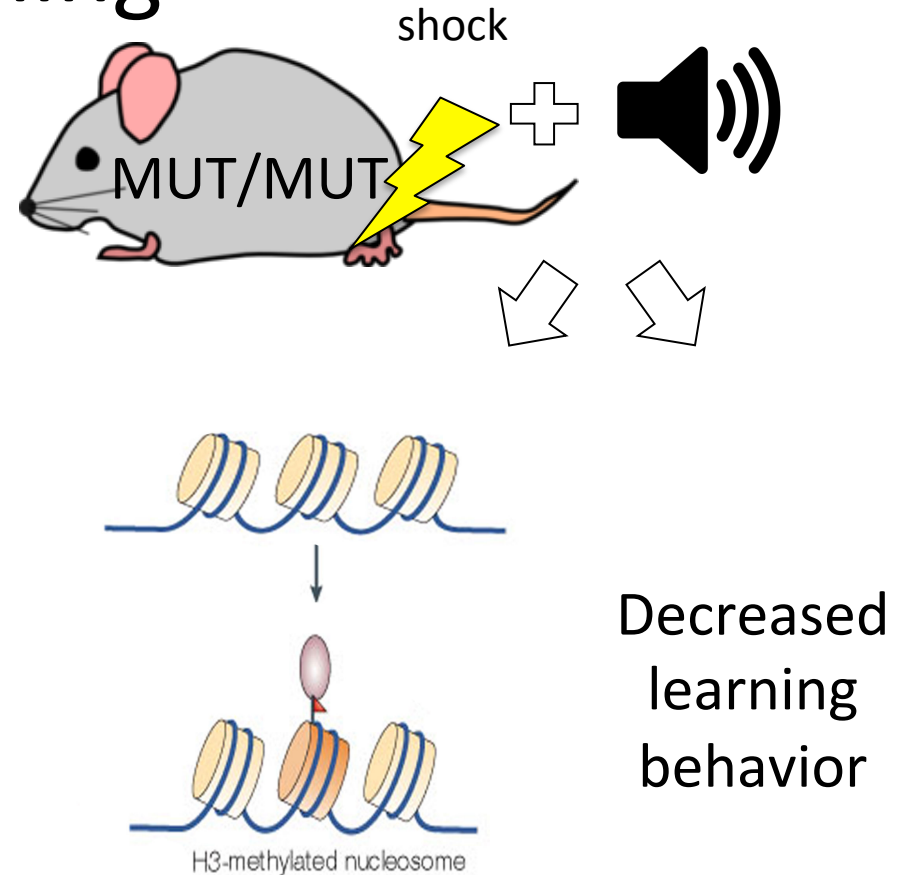
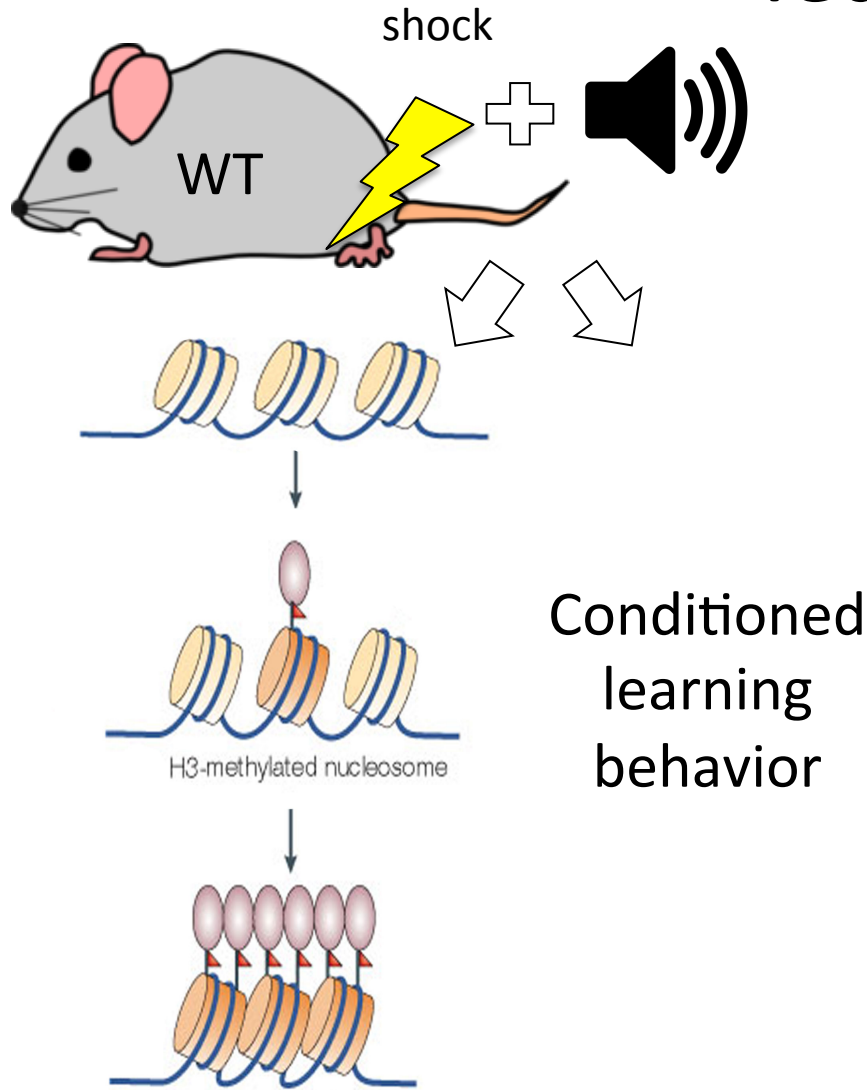
What does **NSD1** do in the cell?



Histone methylation is related to learning

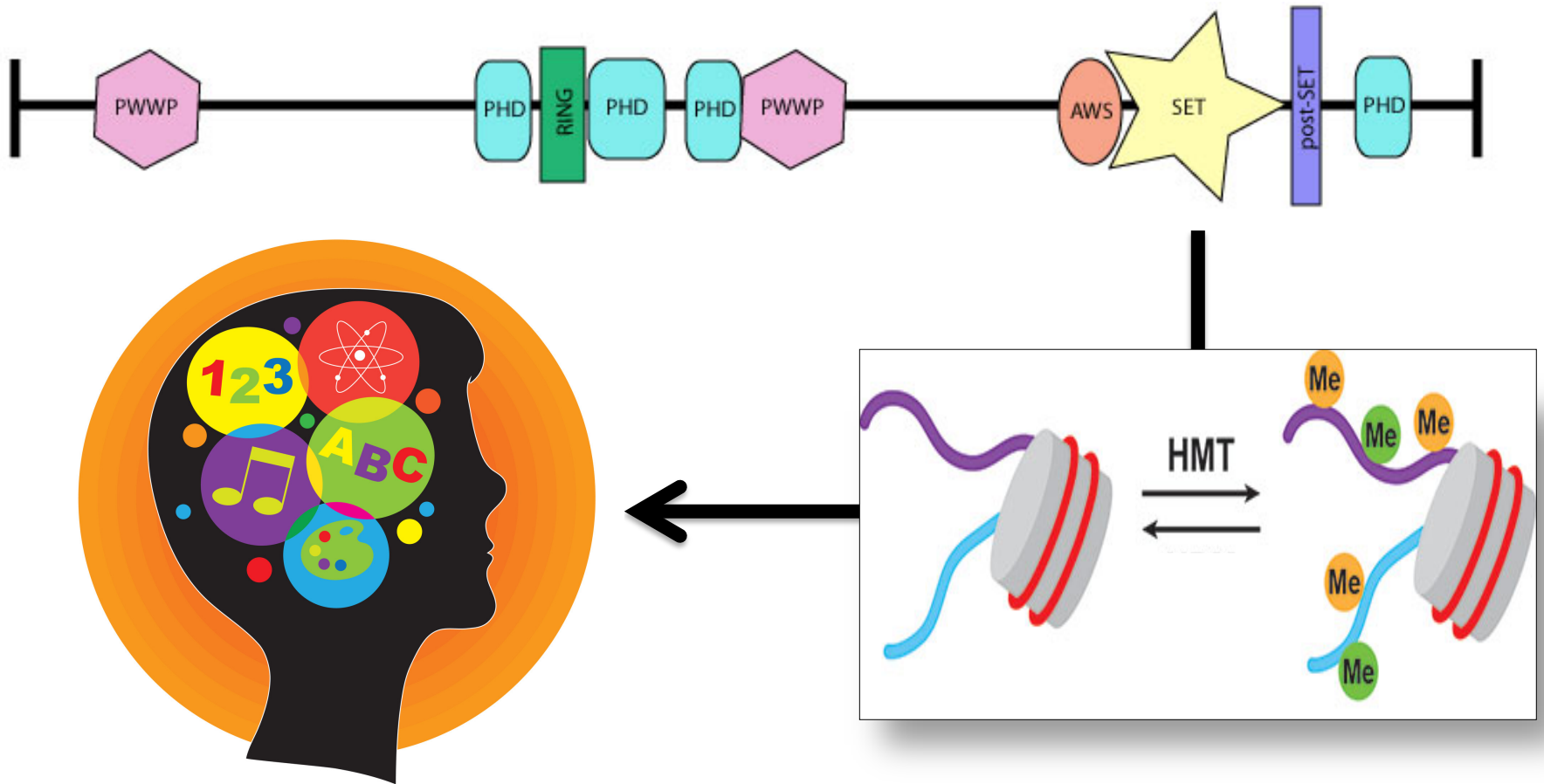


Histone methylation is related to learning



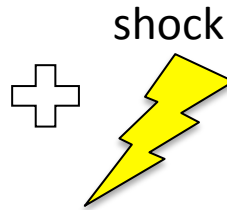
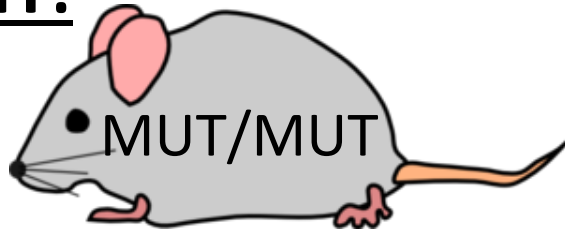
GAP: NSD1's function in learning is unknown

Overall Hypothesis: SET domain in NSD1 has a significant contribution to learning.



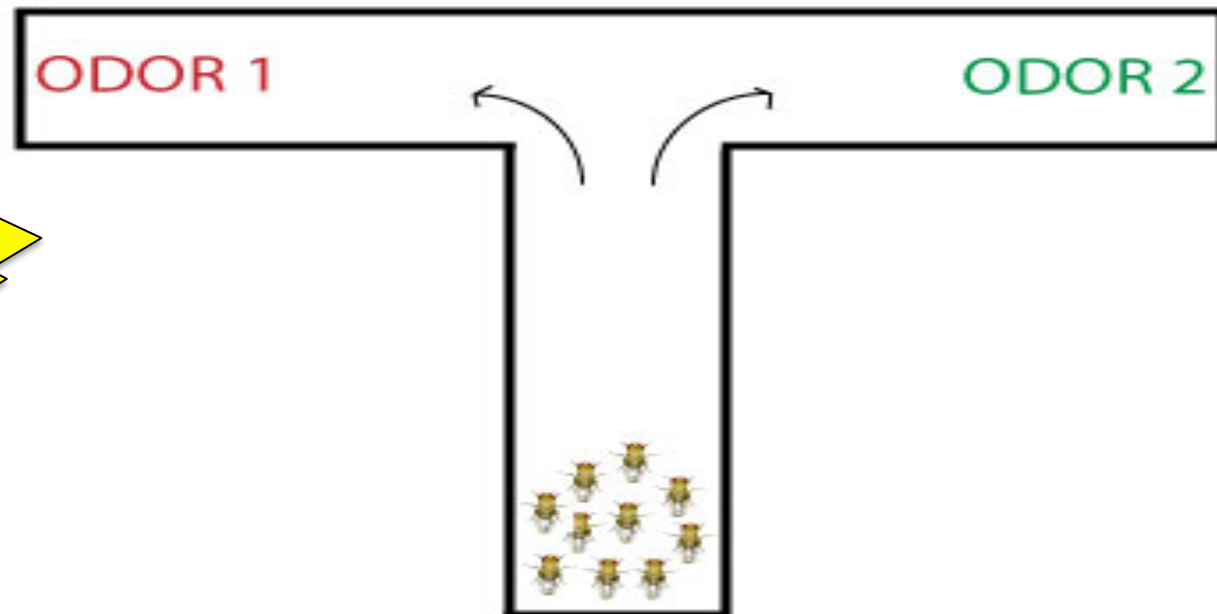
Aim 1: To determine which domains in NSD1/Mes-4 contribute to learning

WHY:



→ DECREASED LEARNING

HOW: Structure function analysis in *Drosophila* Mes-4 with learning assay

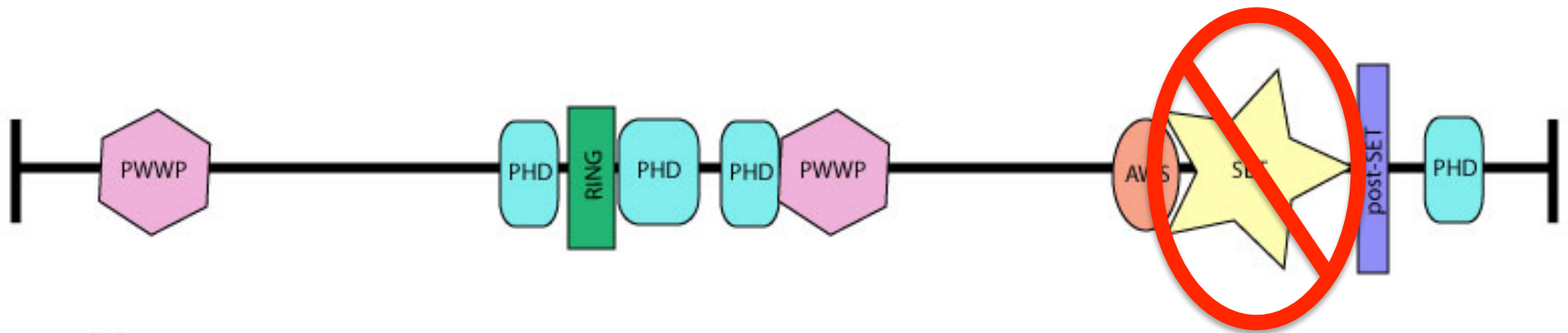


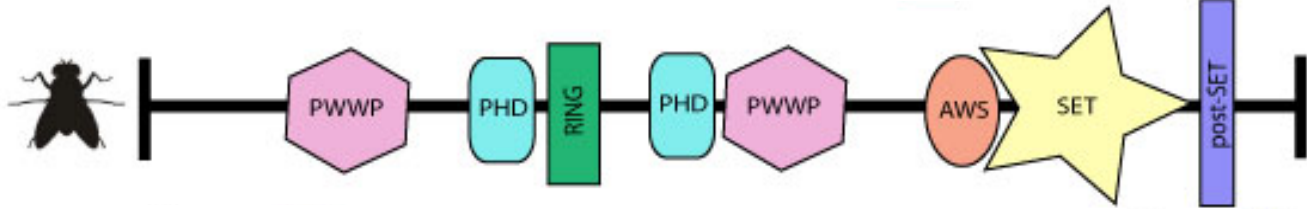
ODOR 1 = SHOCK



ODOR 2 = nothing

AIM 1 HYPOTHESIS: Mutation in SET domain will have the most profound effect on learning impairment

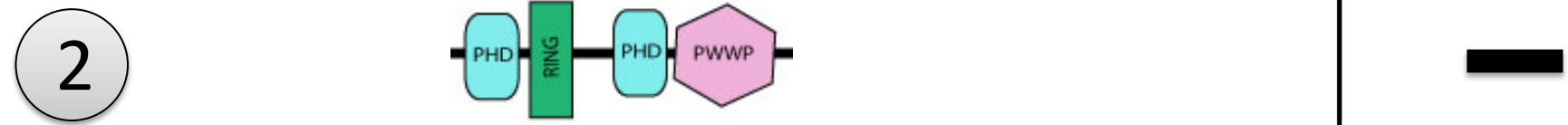




LEARNING



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Aim 2: To determine which genes and proteins are necessary for learning

WHY: To identify all genes and proteins involved with learning and note domain similarities

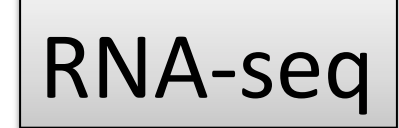
2a.



2a.

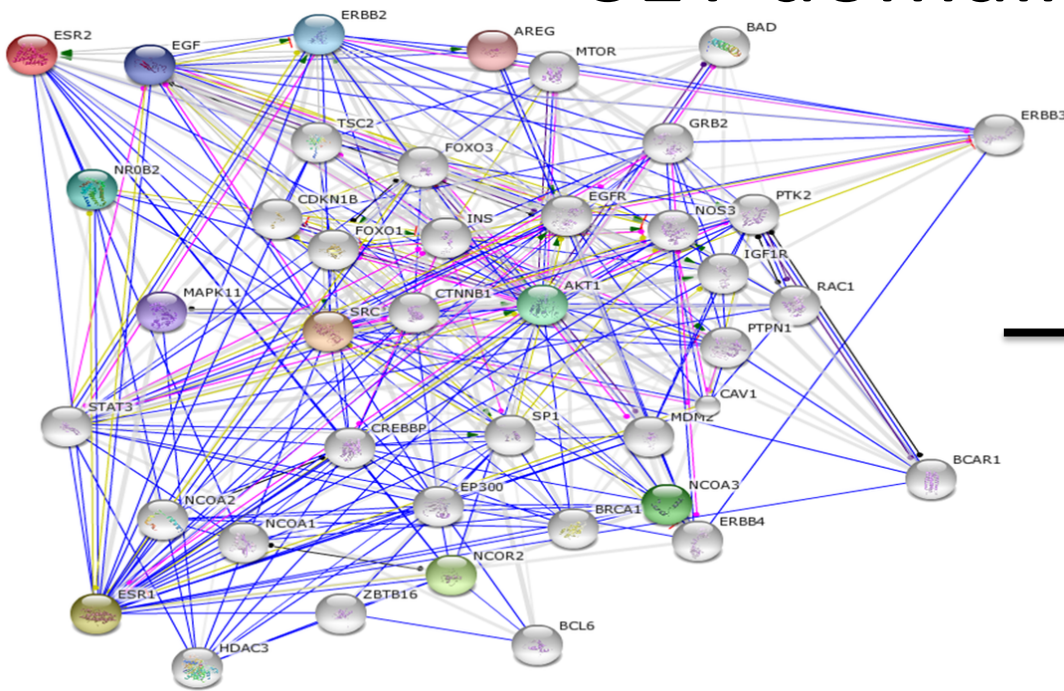


2b.

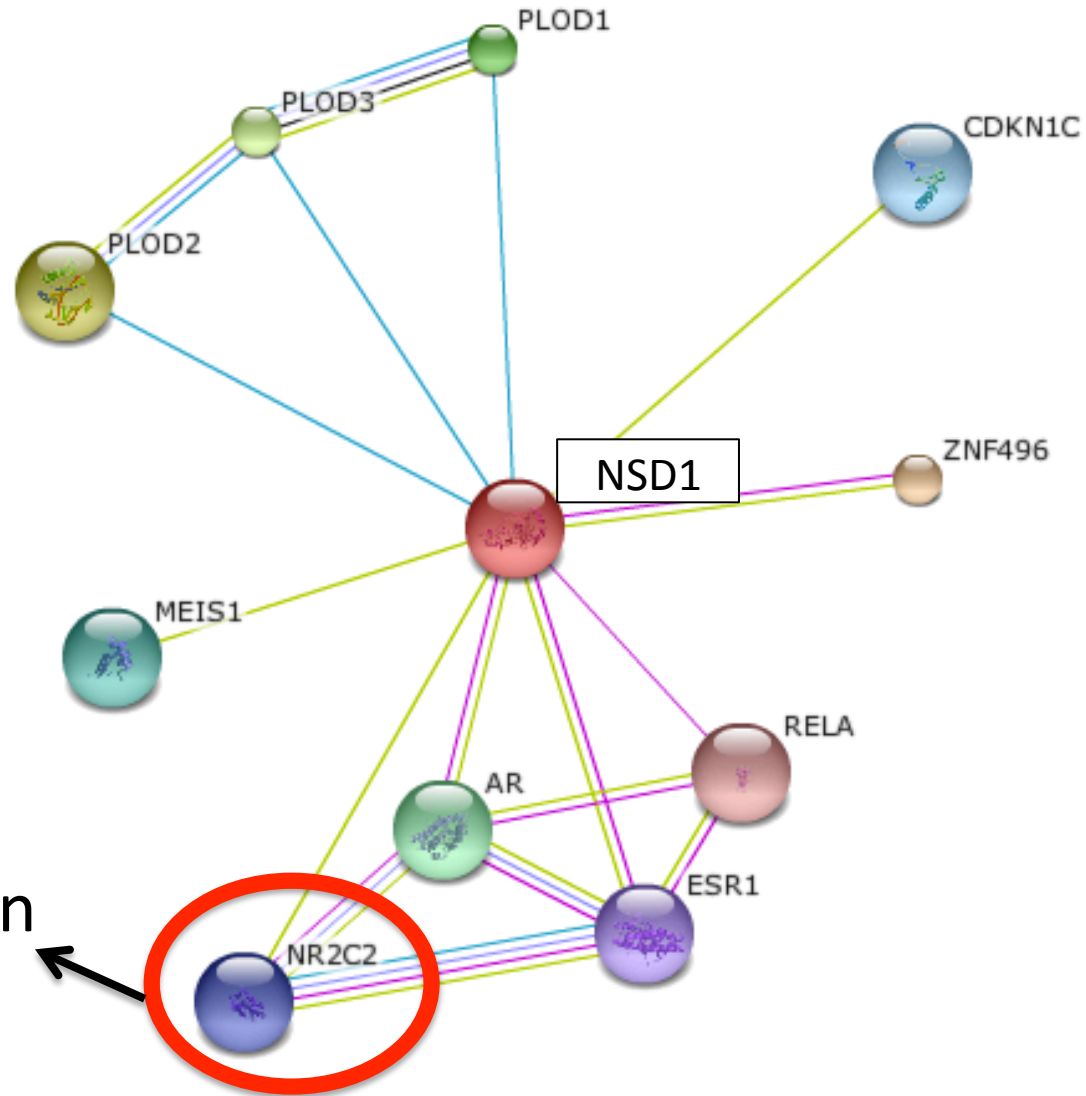


HOW: Use STRING to identify interacting proteins with NSD1 involved in learning, SMART to find domains, identify new genes using RNA-seq, knockout and assay

AIM 2 HYPOTHESIS: There are a wide variety of other proteins and genes associated with learning, most have SET domains



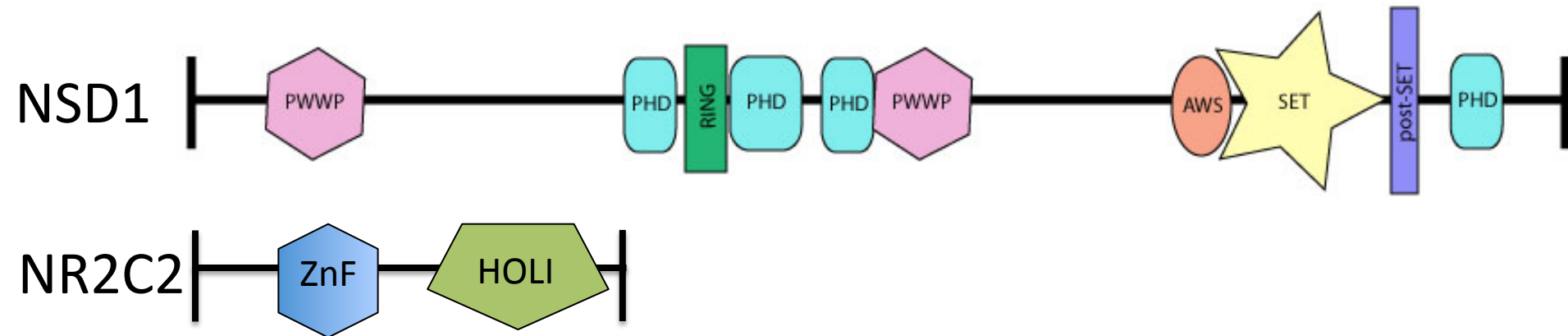
Aim 2a: To determine which proteins are necessary for learning



NR2C2:

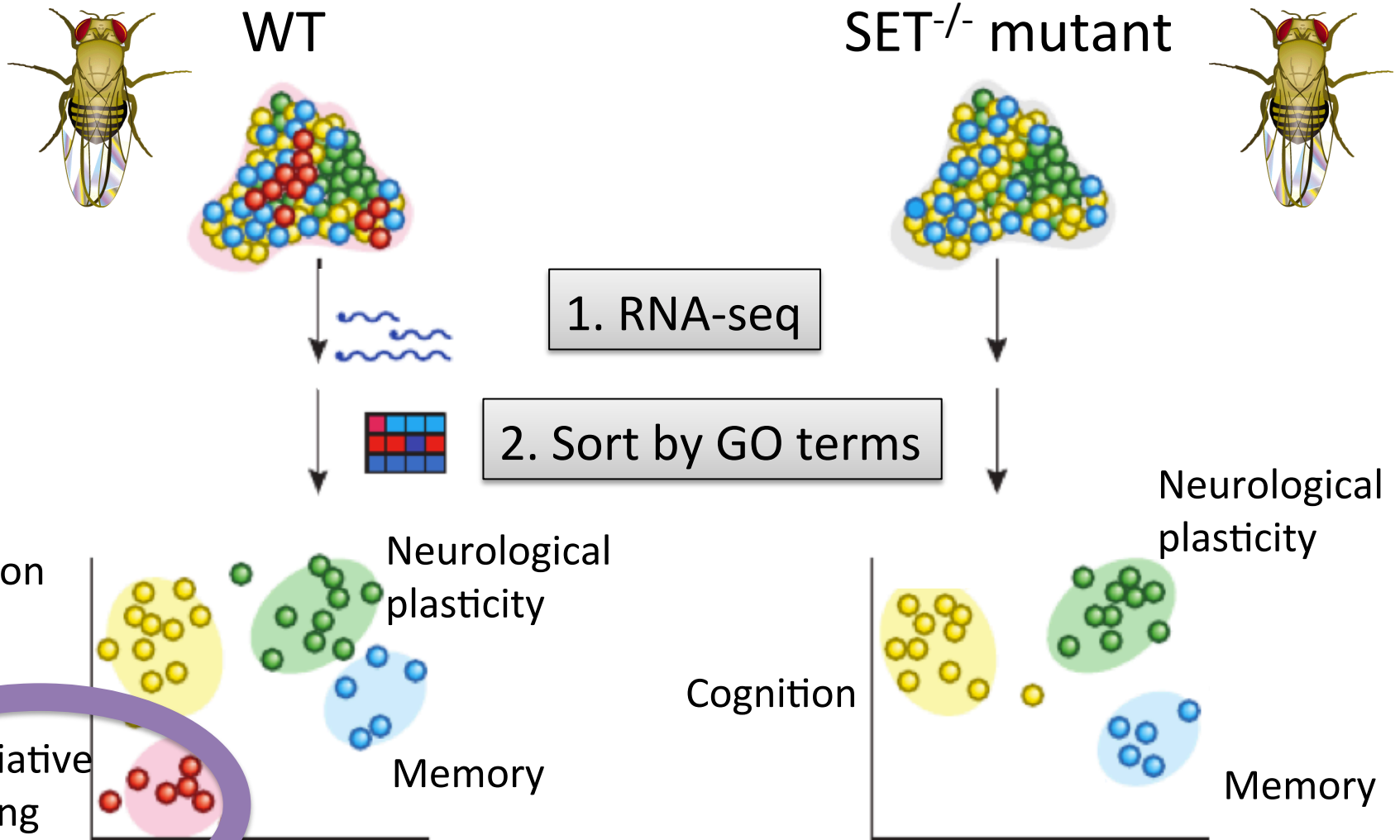
Behavior regulation

Aim 2a: Are there SET domains in NR2C2 like in NSD1?

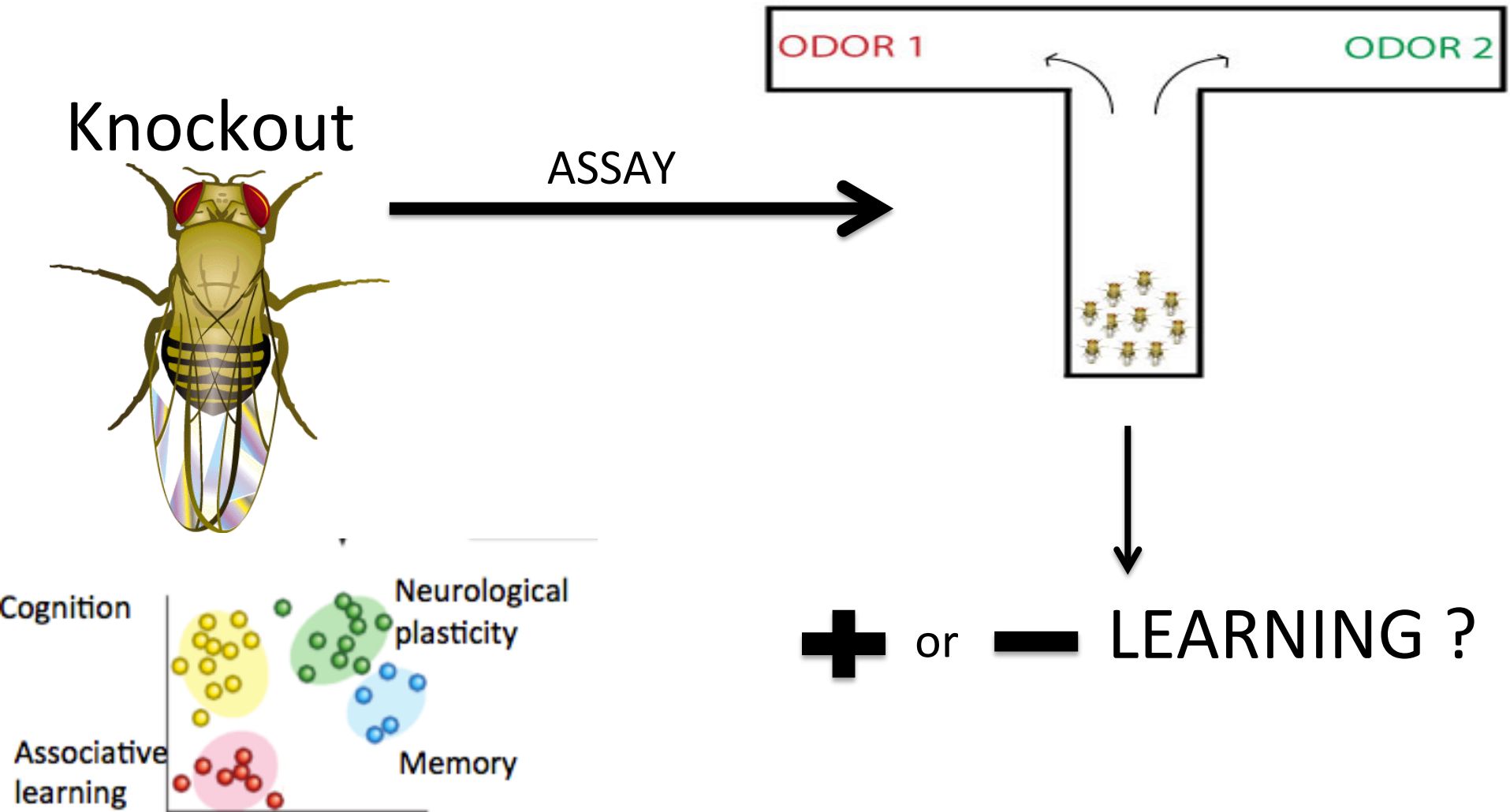


Results: SET domain isn't important for learning, but DNA binding domains are

Aim 2b: To determine which genes are necessary for learning



Aim 2b: Screen genes important for learning



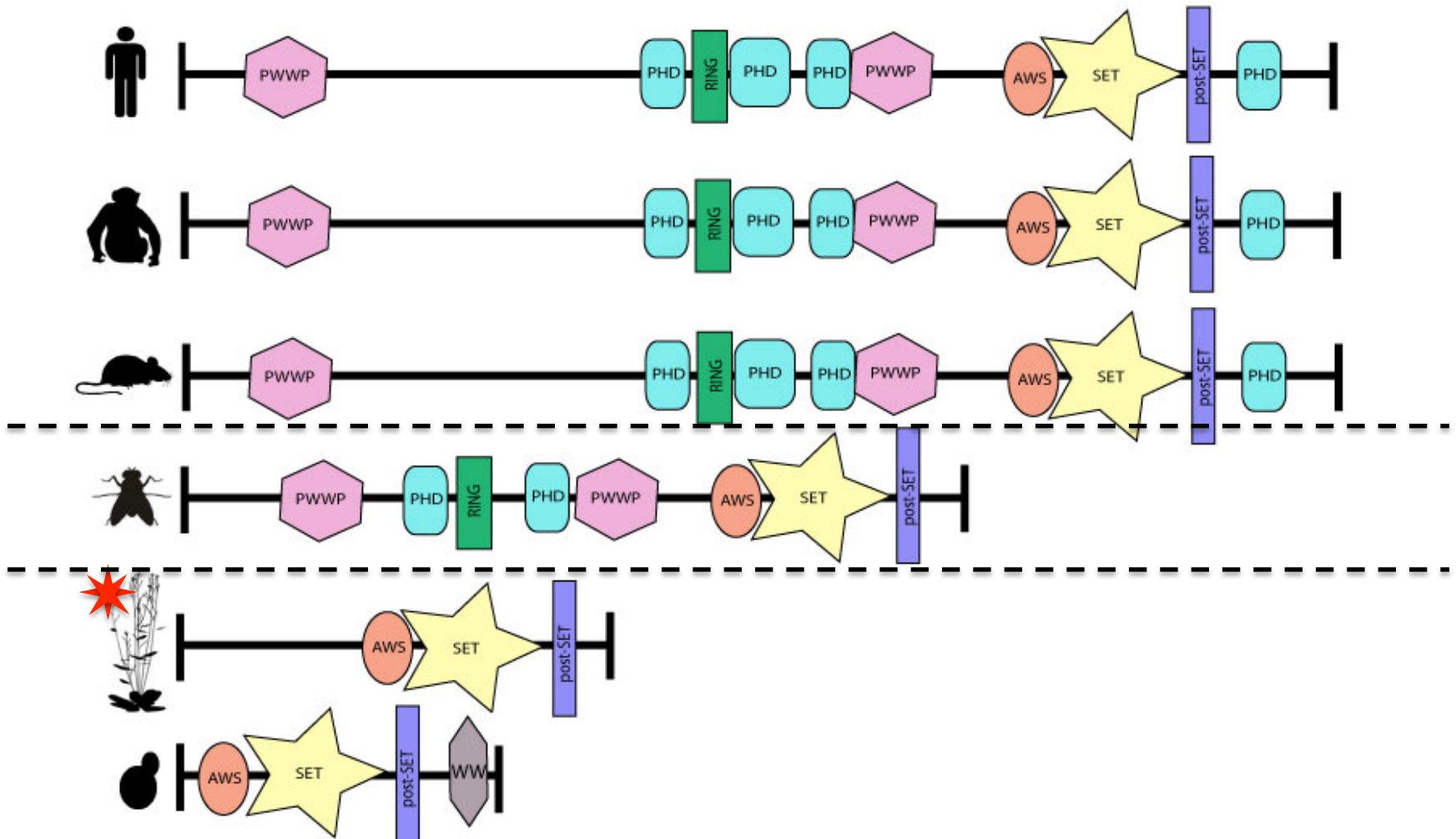
Aim 3: Identify the conserved amino acids important for learning in mammals

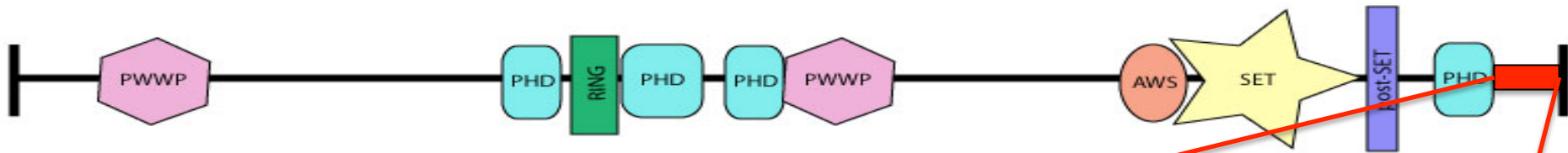
WHY: To identify amino acids unique to species with complex nervous systems



HOW: Clustal Omega, organized by species type

AIM 3 HYPOTHESIS: Mammals have a different set of amino acids for learning in SET domain



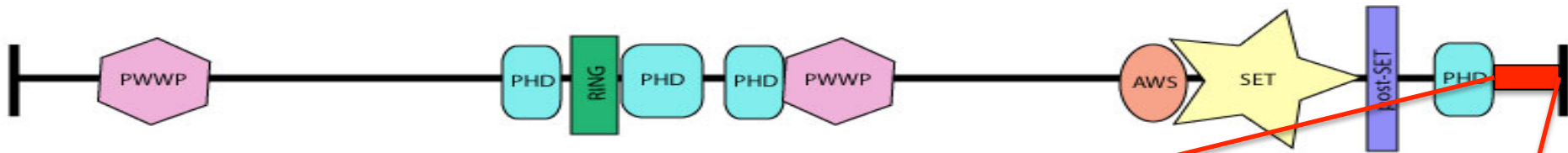


Clustal Omega

ASHH2_ARABIDOPSIS	VKFERFQSGKKCYGLFLLEDVREQQLIEYVGEVLDMQSYETRQKEMAFKGQKHFYFMTL
SET2P_YEAST	APIAIFKTKHKCYGVFAEQDIEANQFIYEYKGEVIEEMEFRDRLIDYDQRHFKHFYFMTL
MES-4_DROSOPHILA	PRLEVVMNERCFGLVNRPIAVQDFVIEYVGEVINHAEFORRMKQIQDRDENYYFLGV
NSD1_MOUSE	PDVEIFRTLQRCWGLFTKTDIKKGEFVNEYVGEVIDEEECRARIRIYQEHGITNFYMLTL
NSD1_CHIMPANZEE	PEVEIFRTLQRCWGLFTKTDIKKGEFVNEYVGEVIDEEECRARIRIYQEHGITNFYMLTL
NSD1_HUMAN	2221 PEVEIFRTLQRCWGLFTKTDIKKGEFVNEYVGEVIDEEECRARIRIYQEHGITNFYMLTL 2280

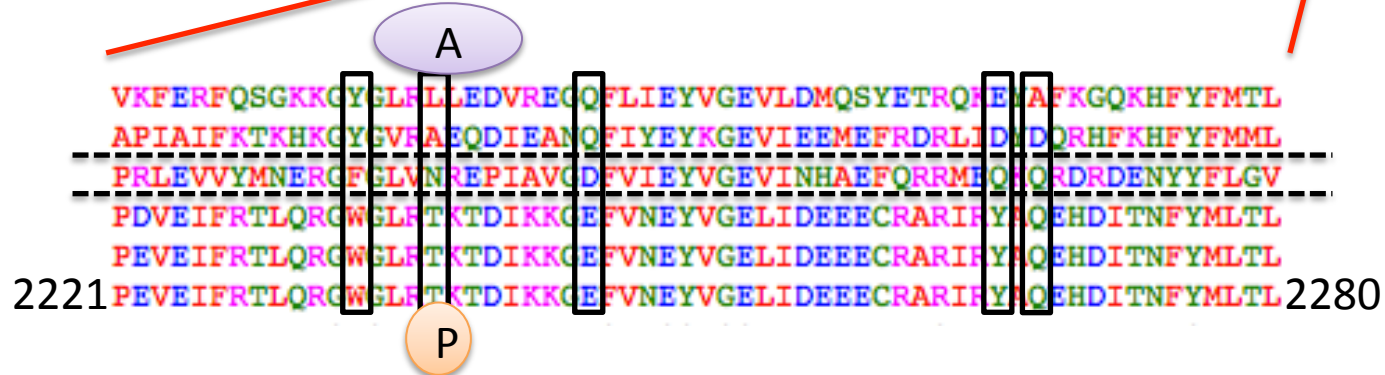
ASHH2_ARABIDOPSIS	NGNEVIDAGAKGNLGRFINHSCEPNQRTFKWVNGEICVGFISMQDLKKGQELTEFDYNYV
SET2P_YEAST	QNGEFIDATIKGSLARFCNHSCSPNAYVWKVVKDKLRMGIFAQRKIIKGEIITFDYNV
MES-4_DROSOPHILA	EKDFIIDAGPKGNLARFMNHSCPNQETQKWTVNCIHRVGFIFAIDIFVNSELTENYLV
NSD1_MOUSE	DKDRIIDAGPKGNYARFMNHCCQPNQETQKWSVNGDTRVGLFALSIDIAGTELTENY
NSD1_CHIMPANZEE	DKDRIIDAGPKGNYARFMNHCCQPNQETQKWSVNGDTRVGLFALSIDIAGTELTENY
NSD1_HUMAN	2281 DKDRIIDAGPKGNYARFMNHCCQPNQETQKWSVNGDTRVGLFALSIDIAGTELTENY 2340

Most matchup- not in noted domain region

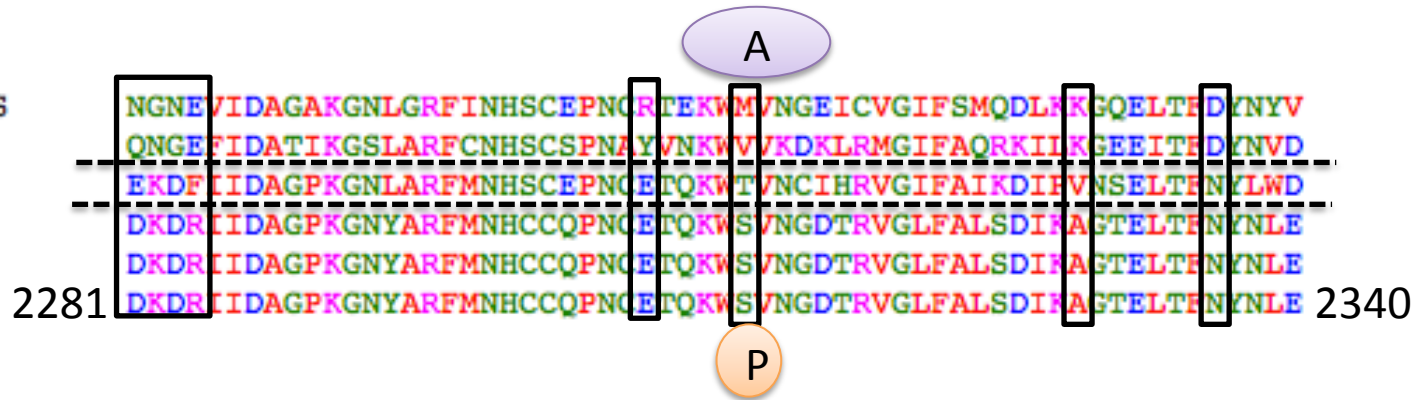


Clustal Omega

ASHH2_ARABIDOPSIS
 SET2P_YEAST
 MES-4_DROSOPHILA
 NSD1_MOUSE
 NSD1_CHIMPANZEE
 NSD1_HUMAN



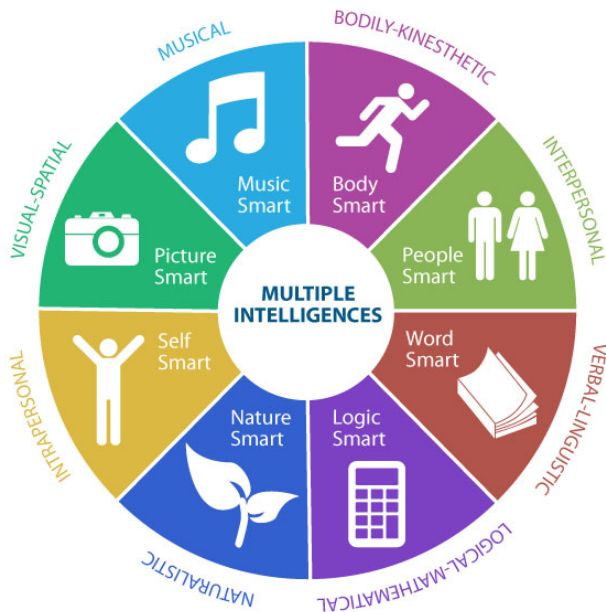
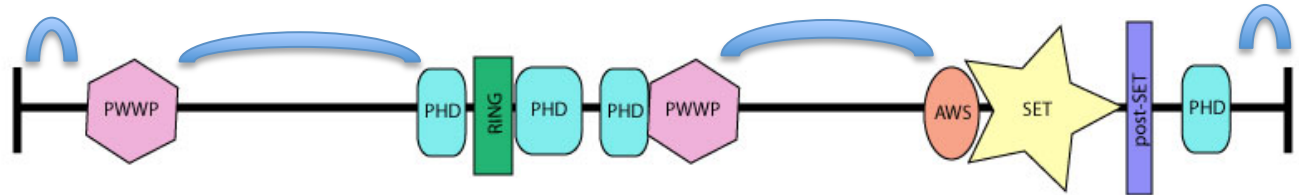
ASHH2_ARABIDOPSIS
 SET2P_YEAST
 MES-4_DROSOPHILA
 NSD1_MOUSE
 NSD1_CHIMPANZEE
 NSD1_HUMAN



Switch amino acids– see what happens?

Future Directions

Further analyze non-domain regions



Determine areas of learning specific to Sotos type impairments

Questions?



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