Sotos syndrome and the \textit{NSD1} gene

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Genetics 564
What is Sotos syndrome?

Impaired Learning

(Turkmen, 2003) Euro J Hum Genet
NSD1 is mutated in Sotos syndrome

GO TERMS

Molecular Function

Biological Process

Cellular Component

Zn$^{2+}$

Histone methylation

Transcriptional Regulation

The Cell Nucleus

Nucleolus

Nuclear Envelope

Nuclear Pores

Chromosomes

Chromatin

Figure 1
How highly conserved is **NSD1**?

<table>
<thead>
<tr>
<th>Animal</th>
<th>Identity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>100%</td>
</tr>
<tr>
<td>Chimpanzee</td>
<td>99%</td>
</tr>
<tr>
<td>Mouse</td>
<td>84%</td>
</tr>
<tr>
<td>Fish</td>
<td>63%</td>
</tr>
<tr>
<td>Chicken</td>
<td>58%</td>
</tr>
<tr>
<td>Drosophila</td>
<td>42%</td>
</tr>
<tr>
<td>Mes-4</td>
<td>36%</td>
</tr>
</tbody>
</table>
How similar are the NSD1 homologs?
What does **NSD1** do in the cell?

Tight Packing

Adapted from (Matouk, 2008) Circulation Research
Histone methylation is related to learning

Adapted from (Sarma, 2005) Nature Reviews Molec Cell Bio
Histone methylation is related to learning

Adapted from (Sarma, 2005) Nature Reviews Molec Cell Bio

**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:**
MUT/MUT + shock → DECREASED LEARNING

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

ODOR 1 = SHOCK

ODOR 2 = nothing

(Barth, 2014) J of Neuro Sci
AIM 1 HYPOTHESIS: Mutation in SET domain will have the most profound effect on learning impairment.
**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. **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.
**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

1. RNA-seq
2. Sort by GO terms

WT

SET^-/- mutant

Cognition

Neurological plasticity

Memory

Adapted from (Sandberg, 2014) Nat Methods
Aim 2b: Screen genes important for learning

Knockout

ASSAY

ODOR 1

ODOR 2

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
Most matchup- not in noted domain region
Switch amino acids—see what happens?
Future Directions

Further analyze non-domain regions

Determine areas of learning specific to Sotos type impairments
Questions?
References:

7. http://circres.ahajournals.org/content/102/8/873/F1.expansion.html
9. http://www.jneurosci.org/content/30/10/3589.long
10. http://www.jneurosci.org.ezproxy.library.wisc.edu/content/34/5/1819.full
12. https://docs.google.com/presentation%2Fd%2F1D8kUW2Fqstx7wdeIRFexUHacCwiORUPIYtbnuSq0Vo%2Fedit&ei=iuZnU_2tH4OoyATw2oKgCw&bvm=bv.65788261,d.aWw&psig=AFQjCNNGww4JK3Uisw6ia9WU1MRk2UhEZfA&ust=1399404391324290
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