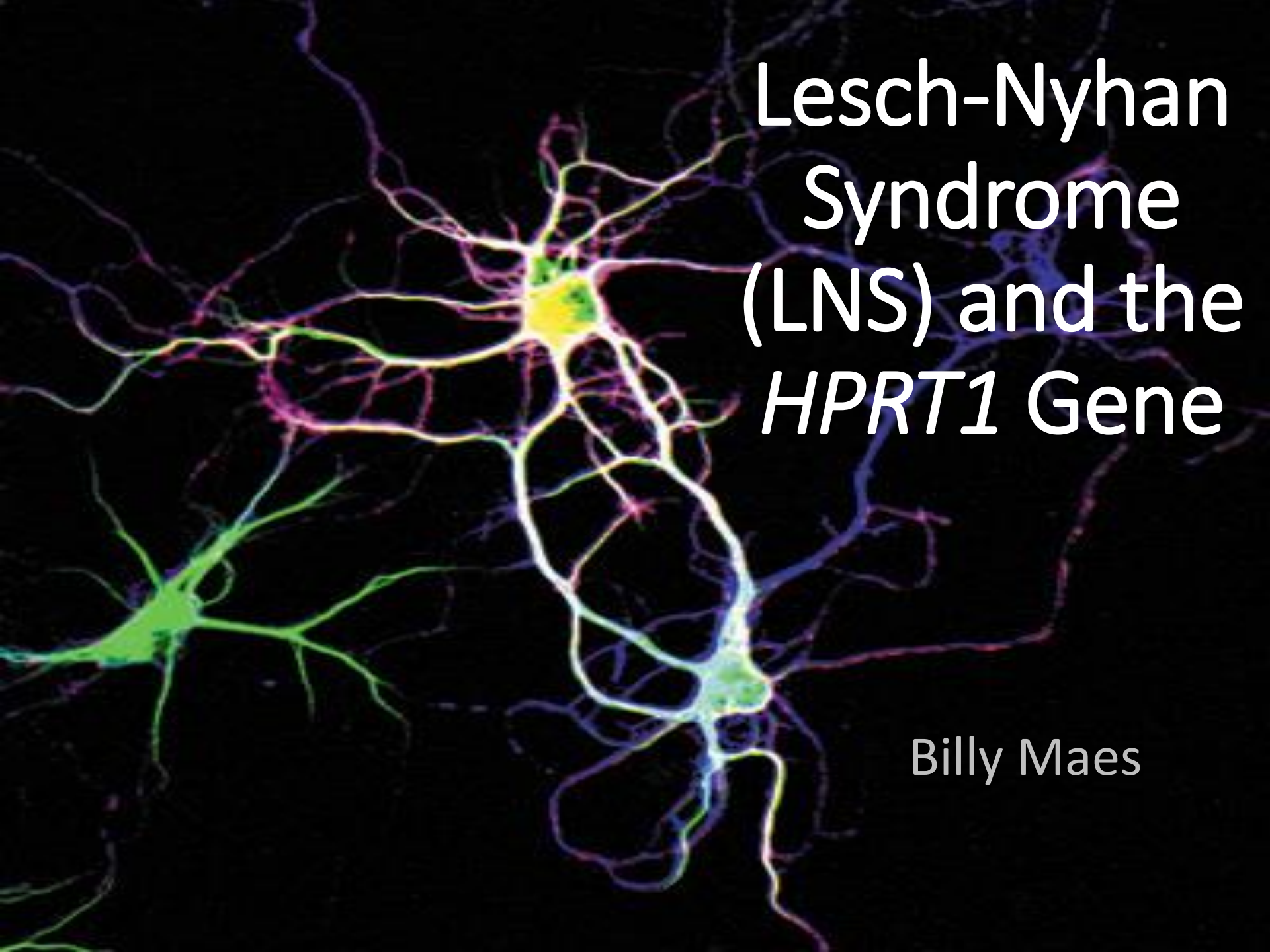
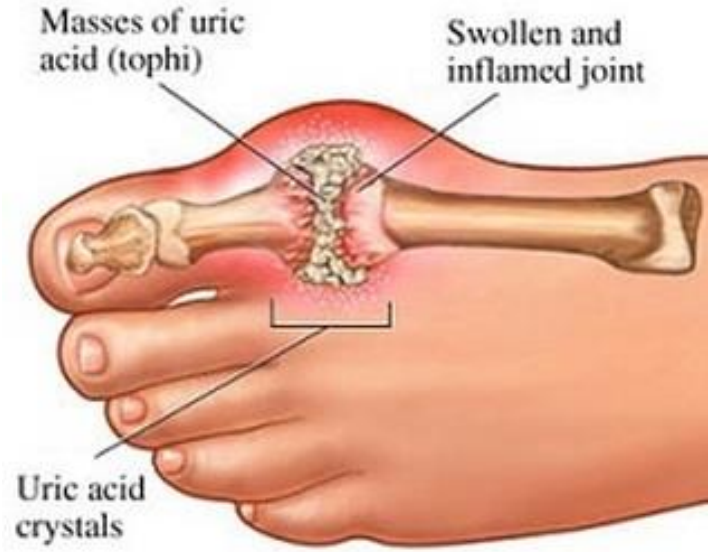
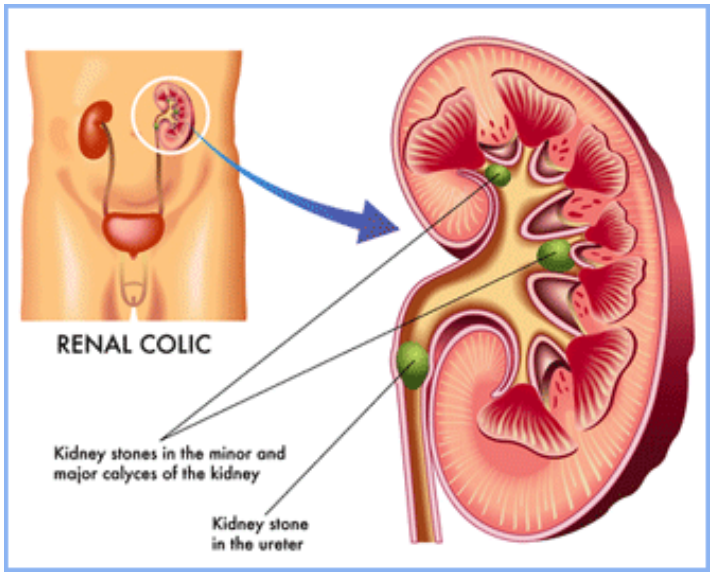


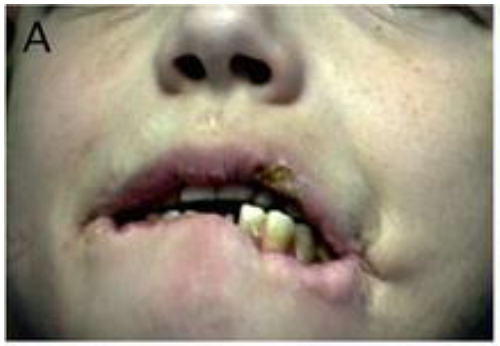
Lesch-Nyhan Syndrome (LNS) and the *HPRT1* Gene

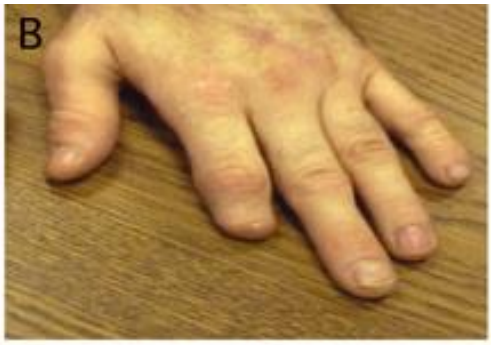
Billy Maes

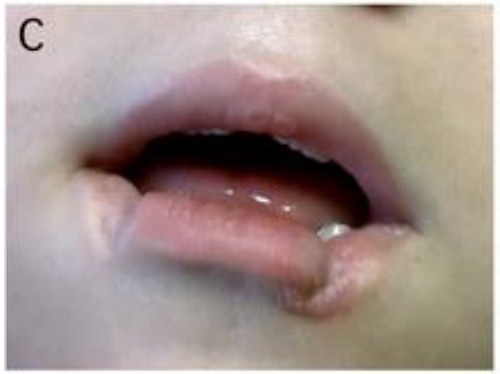
What is Lesch-Nyhan Syndrome?

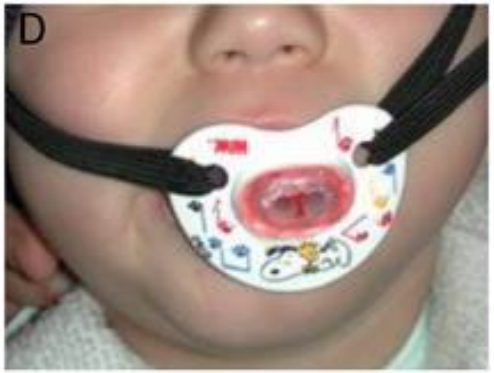


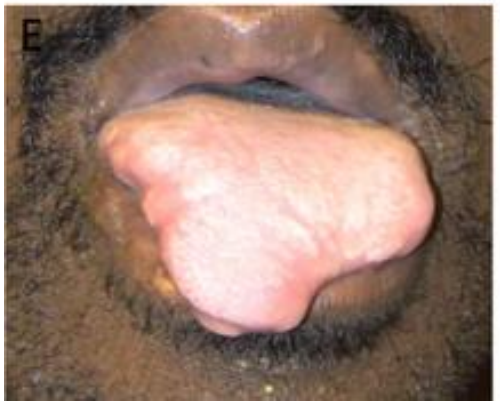


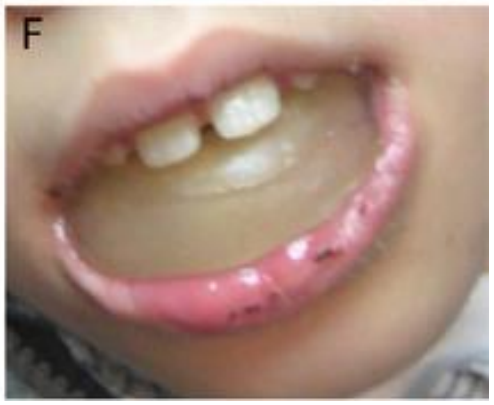




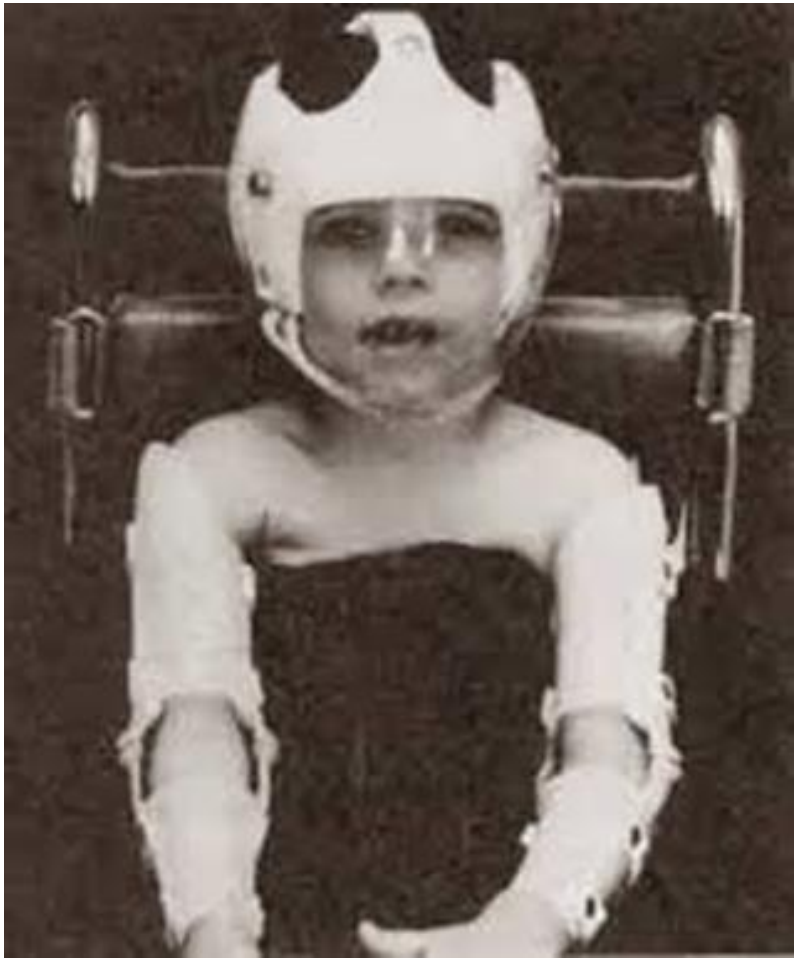






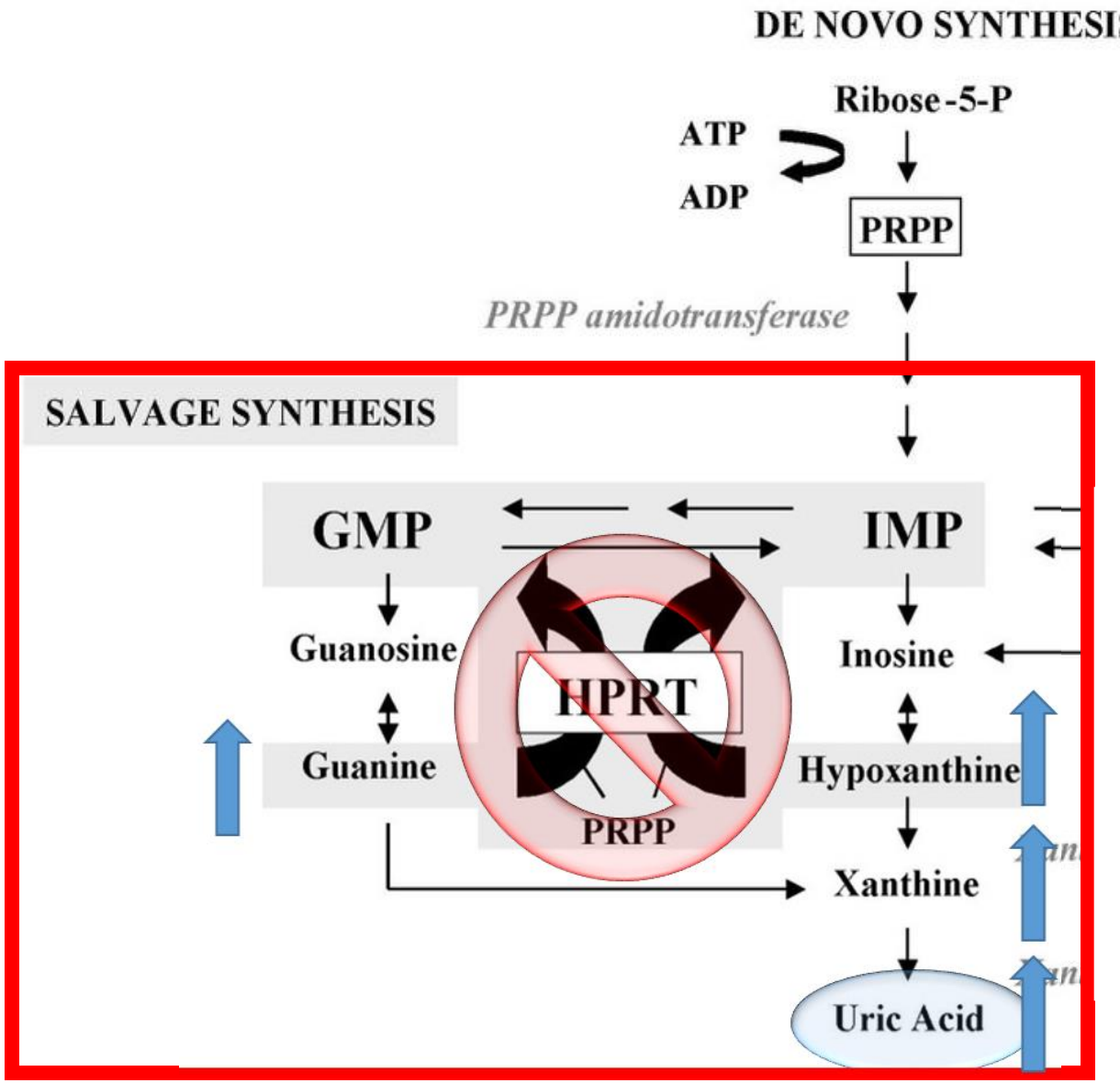


What is Lesch-Nyhan Syndrome?



https://youtu.be/1U6LDpF_LFE?t=58s

What causes Lesch-Nyhan Syndrome?

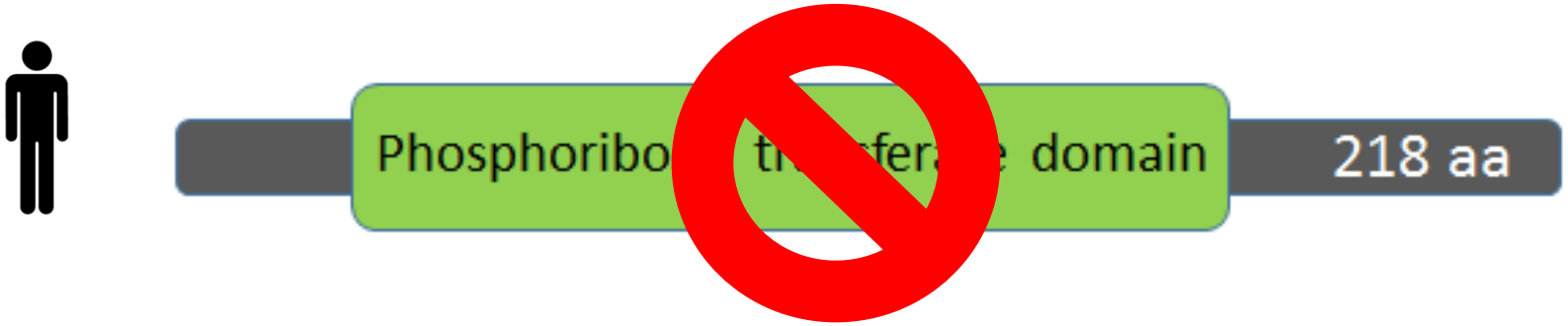


**Unknown mechanism → neurological symptoms

Excess uric acid → gout and kidney stones

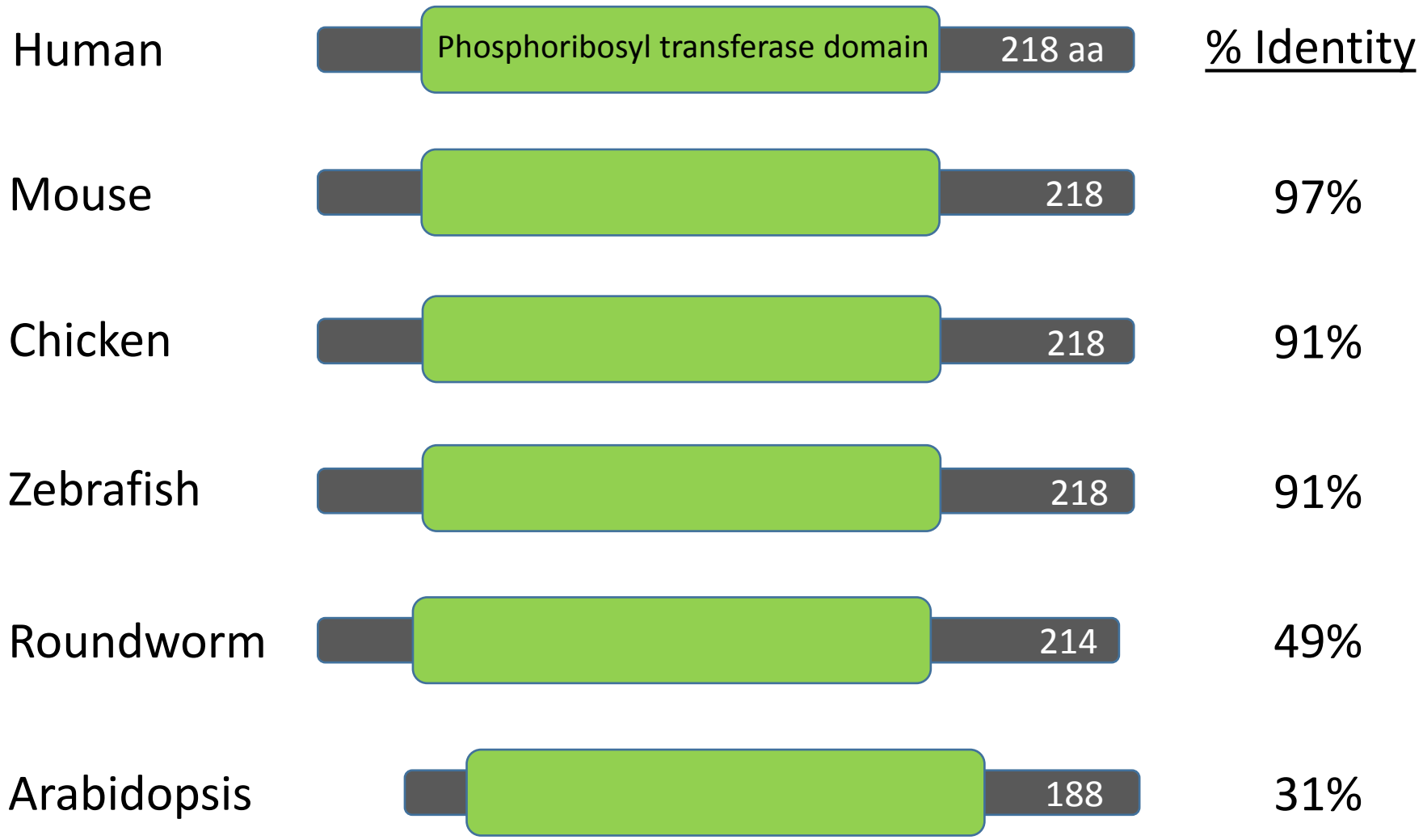
>300 mutations in *HPRT1* are known to cause LNS

Point mutations
Loss-of-function mutations
Change in size, shape



HPRT protein

How well conserved is HPRT?



What are *HPRT1*'s GO terms?

Biological Processes

Neuron development and differentiation

Purine Salvage Pathway

Dopamine metabolism

Dendrite morphogenesis

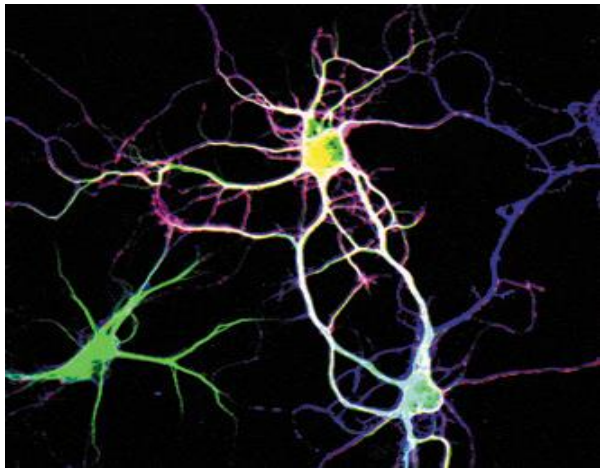
Locomotory behavior

Molecular Functions

Nucleotide binding

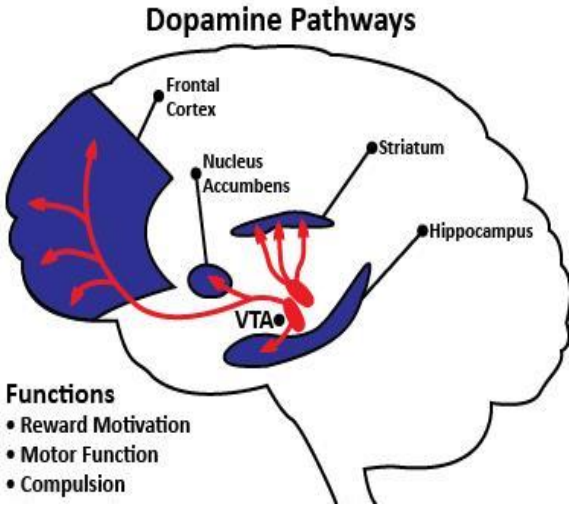
Phosphribosyltransferase activity

Magnesium ion binding

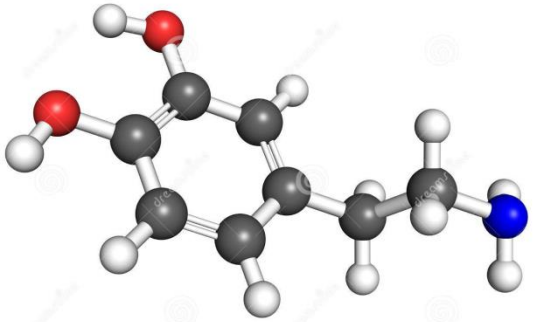


Cellular Components

Cytoplasm



Dopamine



Pleasure

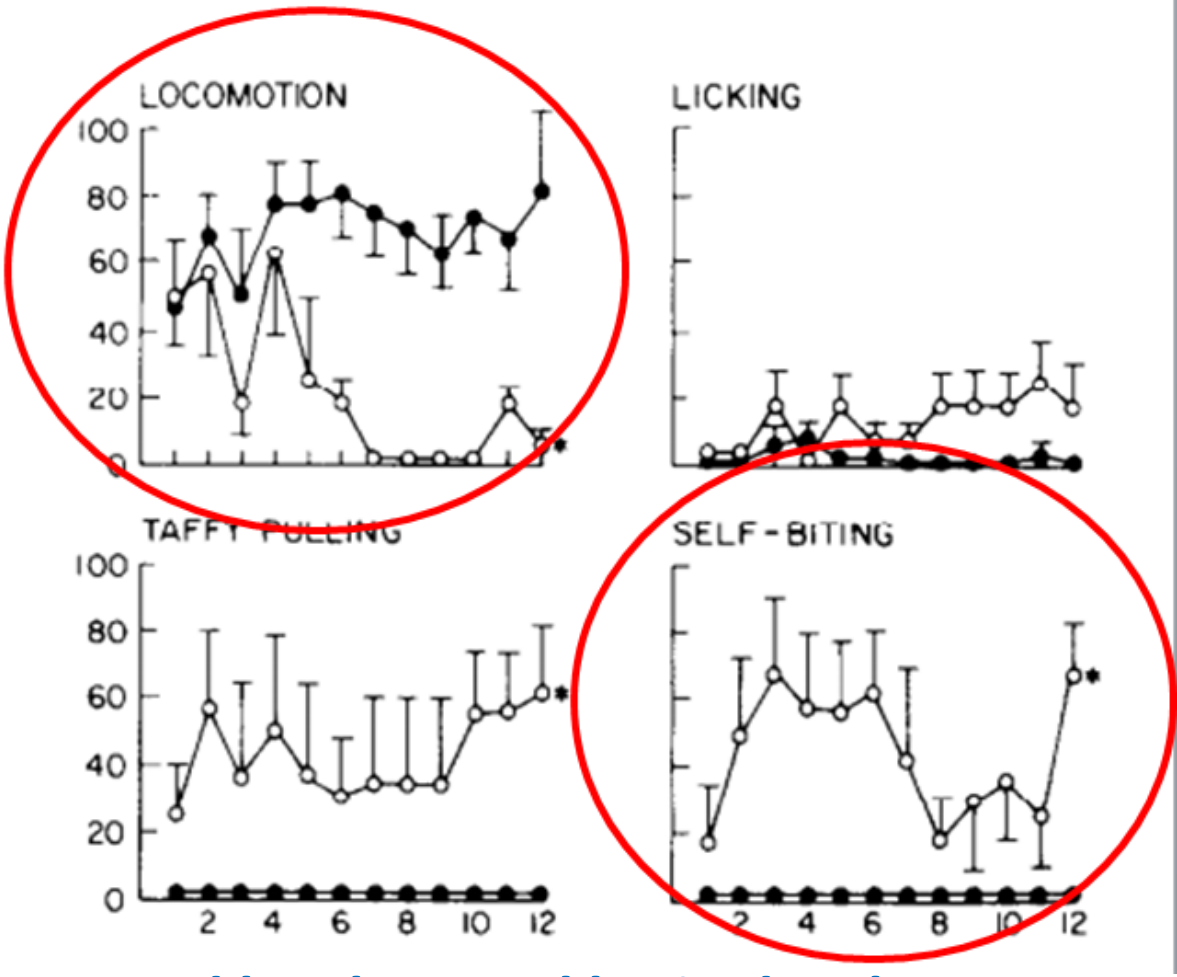
Reward motivation

Motor function

Compulsive behavior

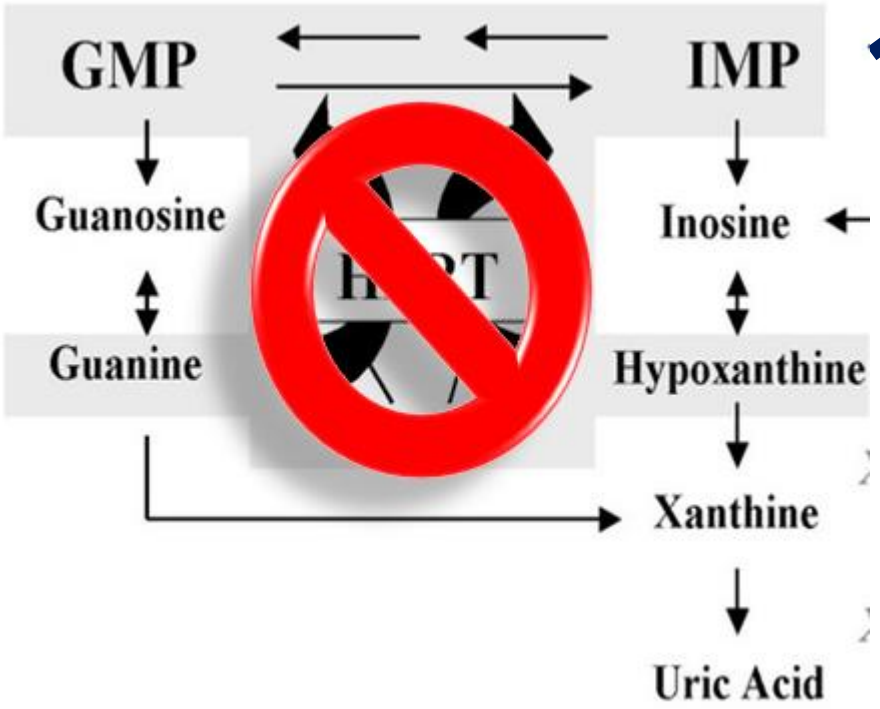
Pharmacological Rat Model

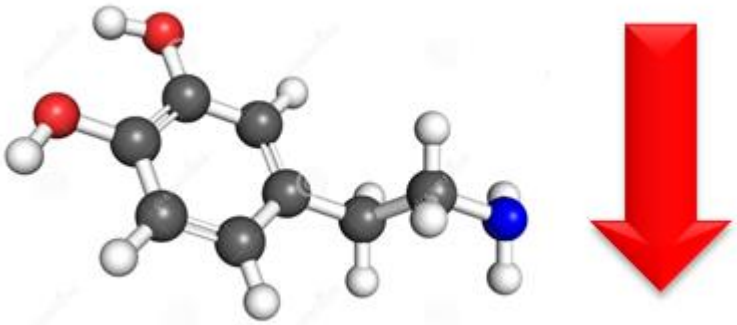
Reduce brain dopamine in neonatal rats using neurotoxin 6-OHDA

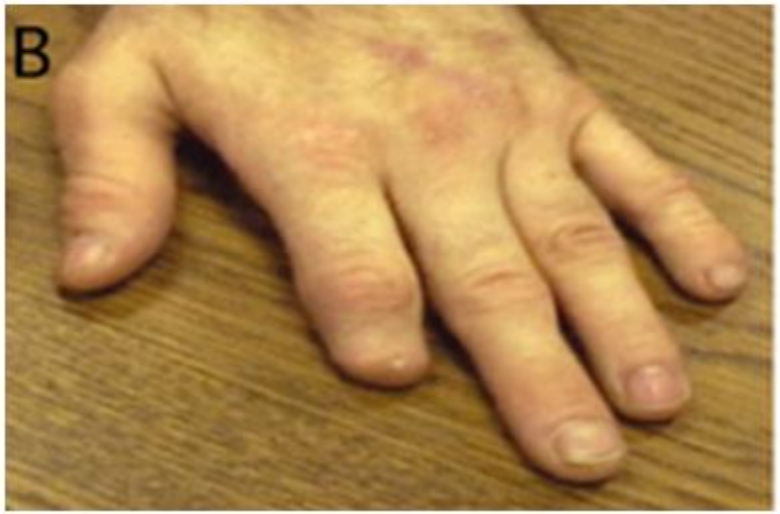


****LNS phenotypes may be caused by abnormal brain development, induced by low dopamine levels neonatally**

Gap in Knowledge

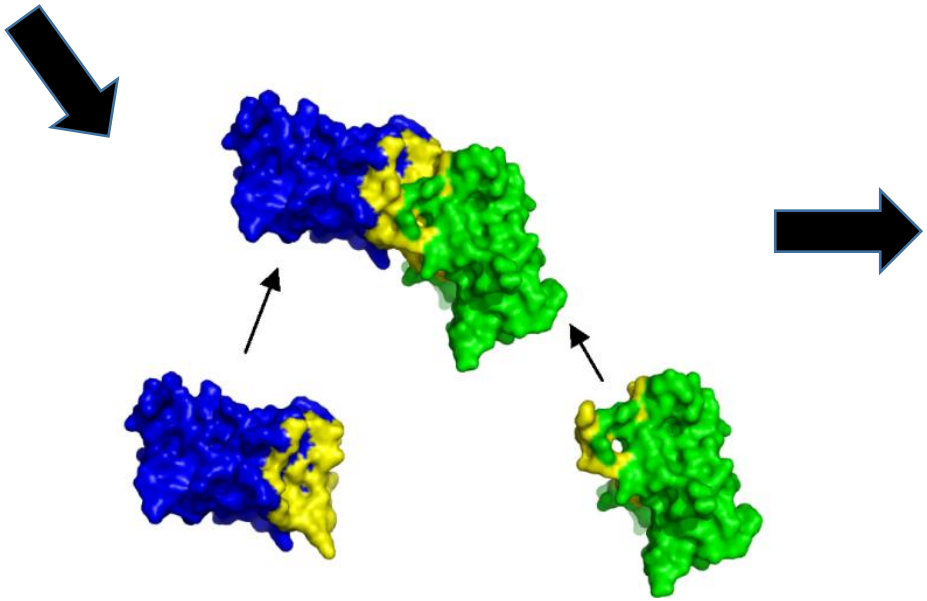


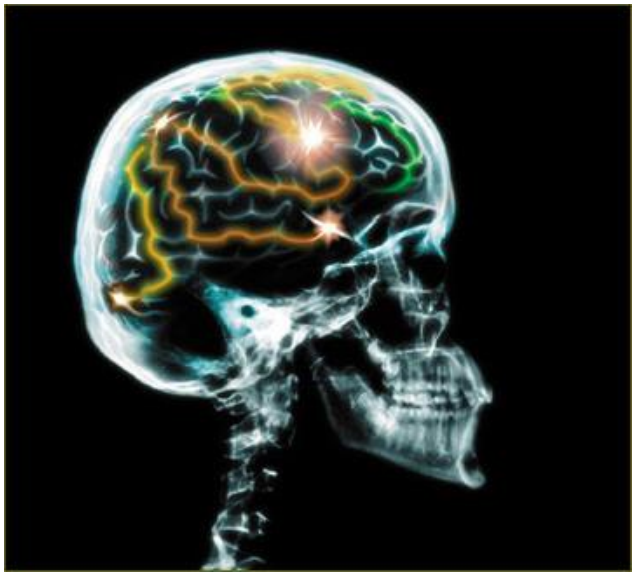




Hypothesis

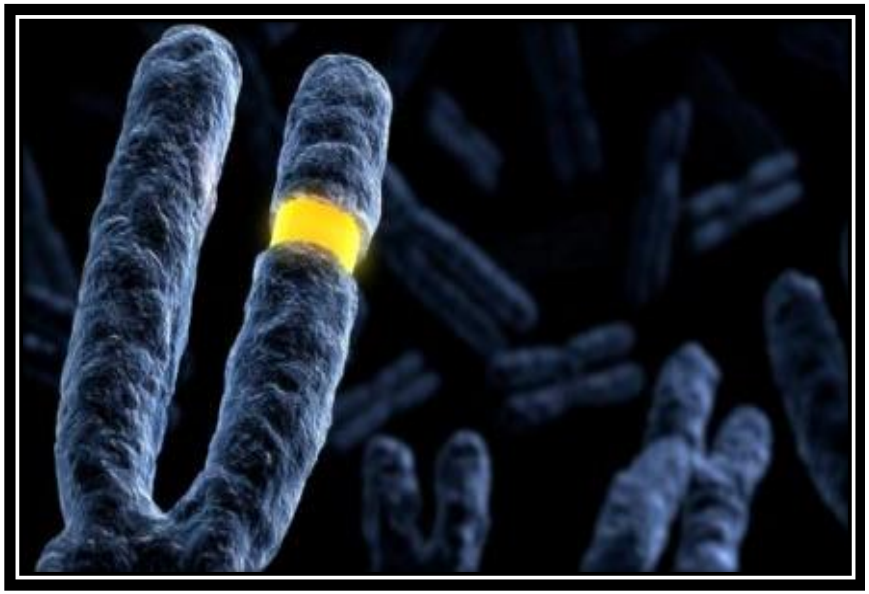
Hypothesis: *HPRT1* regulates the development of the dopaminergic system, important for normal cognition and behavior, through protein interactions in the brain.

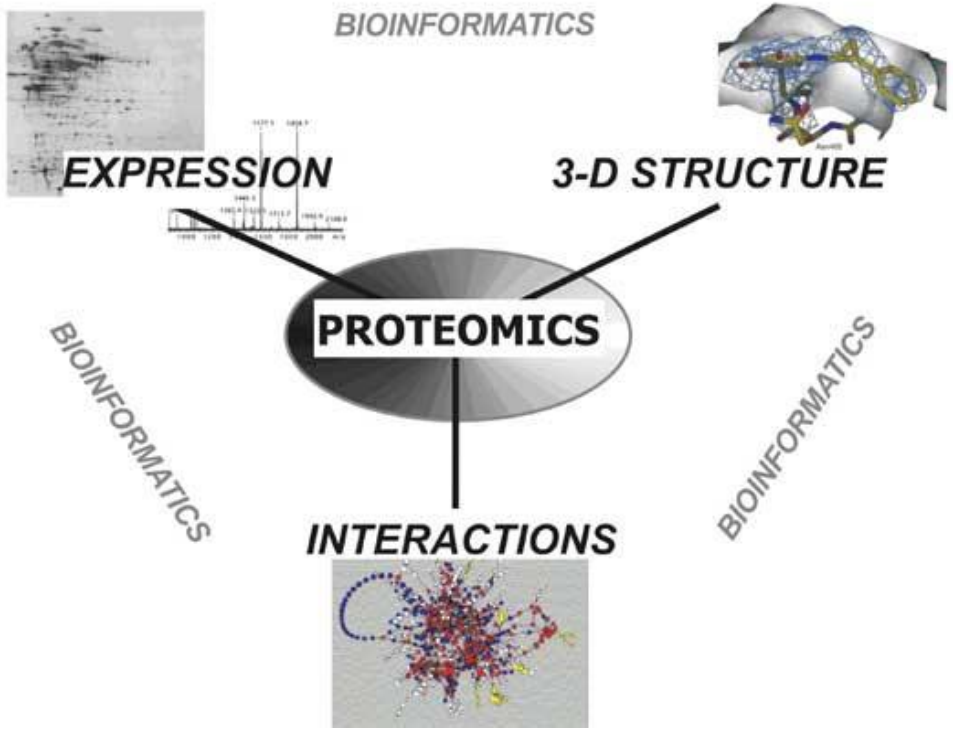




Primary Goal

<u>Primary Goal:</u> Determine the genomic and proteomic changes that contribute to LNS neurological dysfunction as a result of loss-of-function mutations in *HPRT1.*

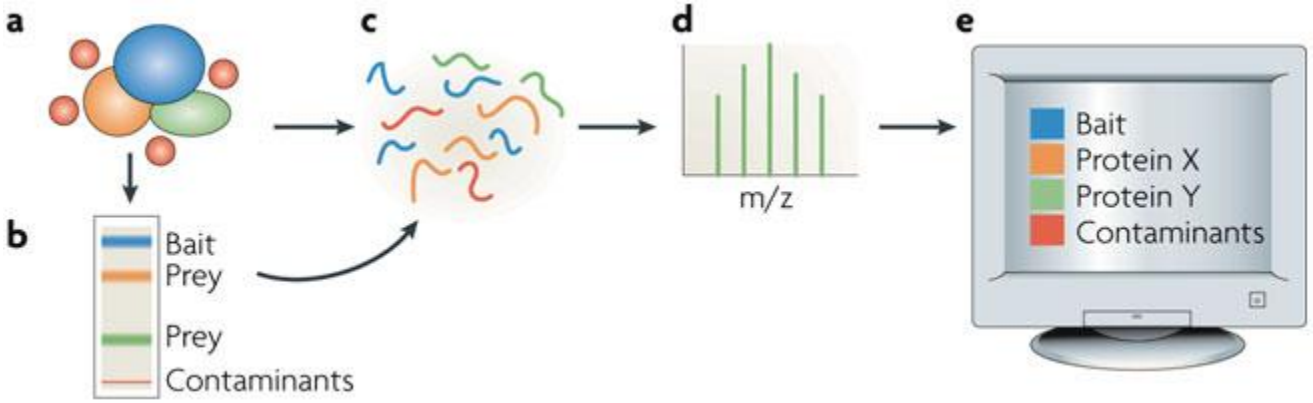




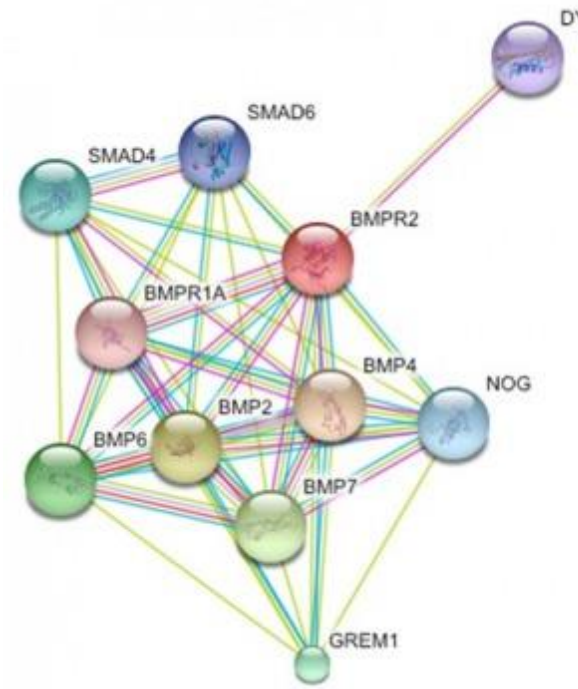
Zebrafish: A Model Organism for LNS

91% identity to human HPRT

Specific Aim #1: HPRT interaction partners



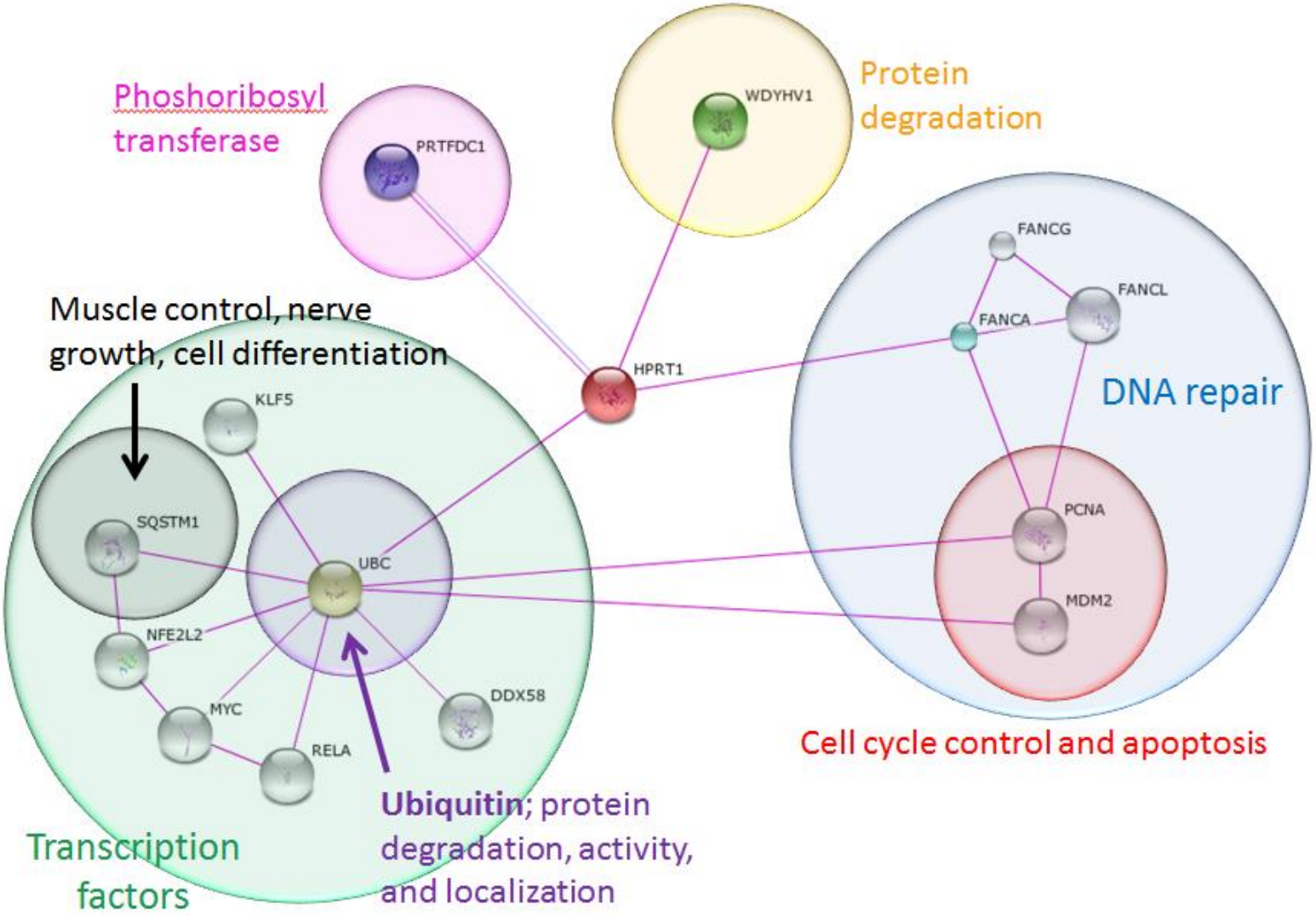
Affinity purification- mass spectrometry (AP-MS)



STRING database

Determine function of HPRT interaction partners

Specific Aim #1: HPRT interaction partners

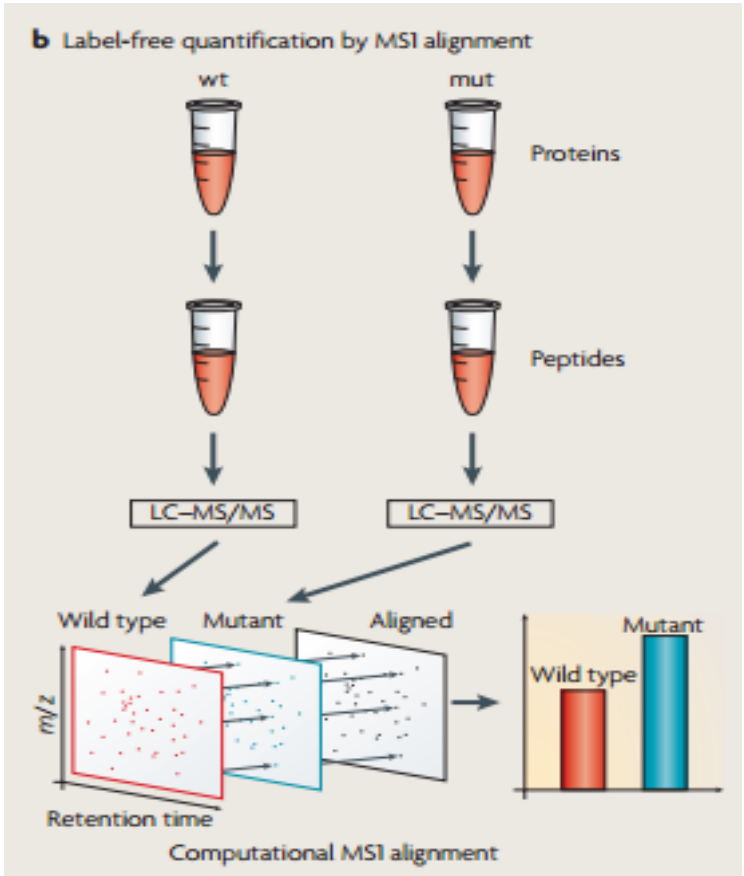


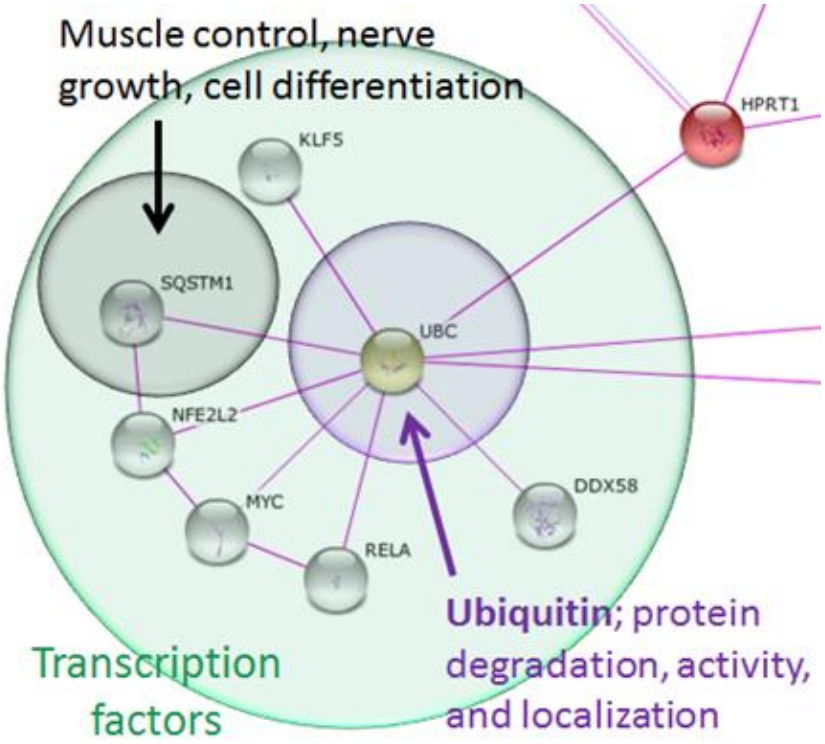
****Hypothesis: SQSTM1 activates NF-KB (synaptic plasticity & dendrite growth), NGF (nerve growth), and titin/TTN (linked to movement disorders)**

Specific Aim #2: Altered Protein levels?

<u>Quantitative mass spectrometry:</u>

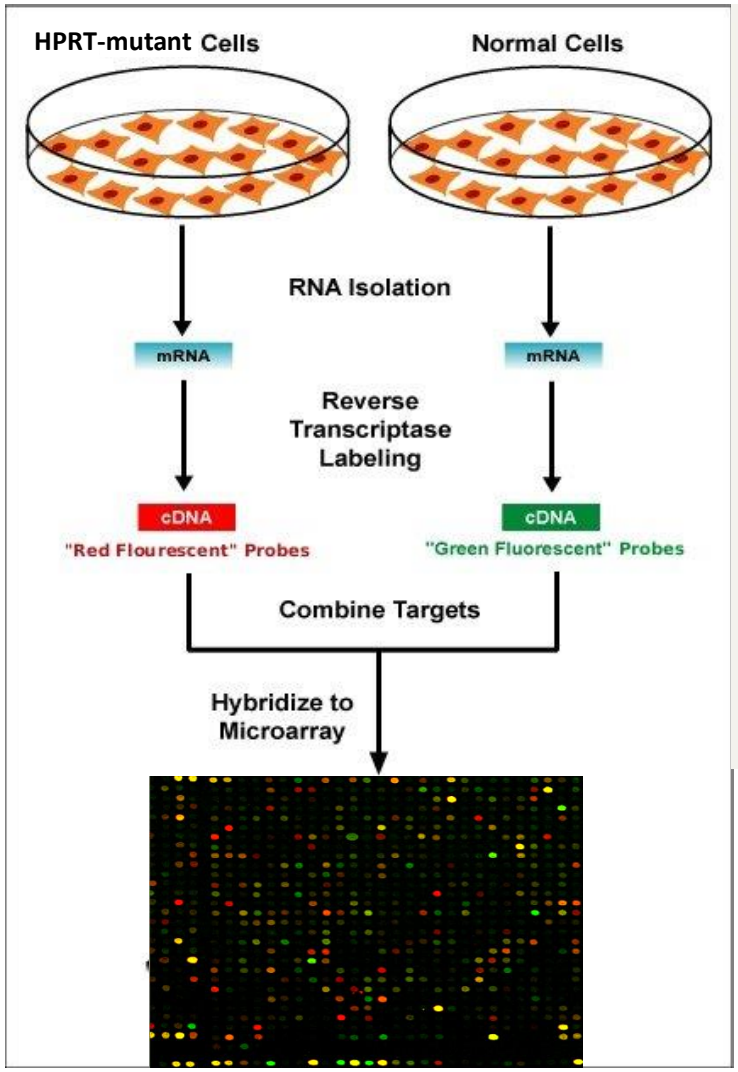
Compare protein levels in wild-type and HPRT-mutant zebrafish

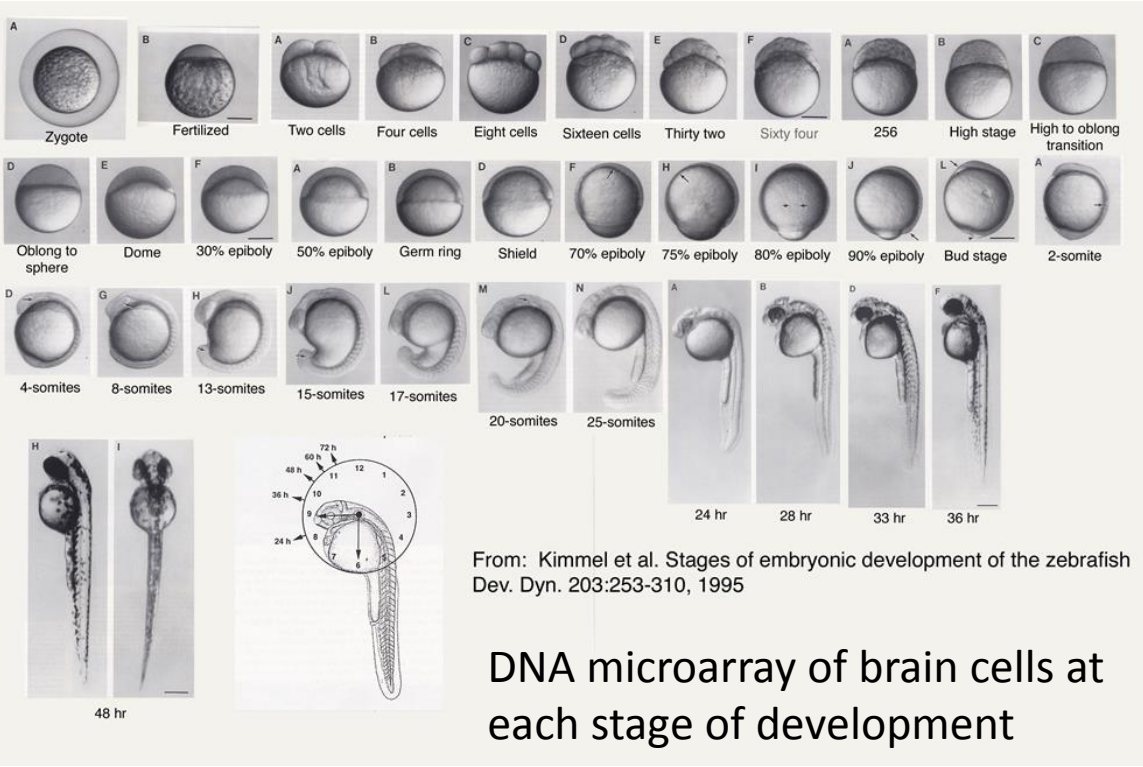




****Hypothesis: SQSTM1 decreases in HPRT mutants**

Specific Aim #3: Altered gene expression during brain development?





From: Kimmel et al. Stages of embryonic development of the zebrafish Dev. Dyn. 203:253-310, 1995

DNA microarray of brain cells at each stage of development

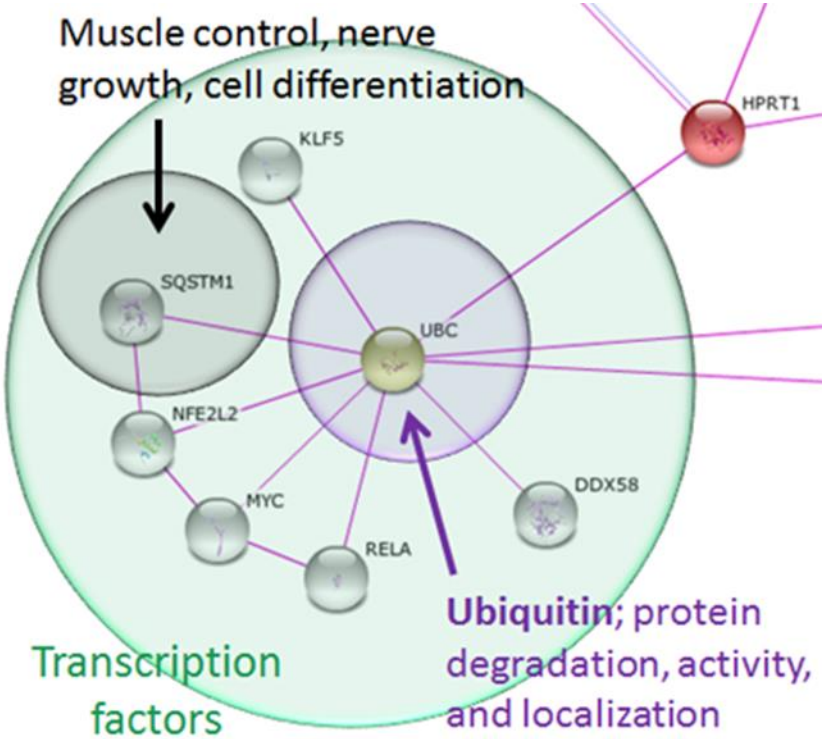
****This will indicate <u>when</u> mutations in *HPRT1* alter neuronal gene function, indicating how brain development may be altered**

Conclusions

Aims: indicate how gene expression and protein interactions change as a result of HPRT mutations.

Gain insight into the mechanisms that lead to the neuronal-behavioral phenotypes of LNS.

Future Directions



Alter levels of SQSTM1 and other proteins that interact with HPRT1. Observe if neurological or behavioral LNS phenotypes appear in mice.

Image URLs and References

1. http://www.gnet.org/wp-content/uploads/explained-got-disease.jpg
2. http://www.keystonekidney.com/images/about-kidney-stones.gif
3. http://simple-health-secrets.com/wp-content/uploads/2013/06/Lesch-Nyhan-Syndrome-4.jpg
4. http://medicalpictures.net/wp-content/uploads/2010/10/Lesch-Nyhan-Syndrome-pictures-3.jpg
5. http://www.ojrd.com/content/2/1/48/figure/F1
6. http://4.bp.blogspot.com/-IZrB3OKIHH8/Uo7dqy5kLSI/AAAAAAAAABA/2ahaXRkqelg/s72-c/leshnyhan.jpg
7. http://www.movementdisorders.org/MDS-Files1/Journals/Images/CPJ-Volume-1-Issue-3/mdc312040-fig-0001.png
8. http://www.cdb.riken.jp/jp/04_news/annual_reports/2006/WebHelp/common/lab1_07hlfig2.htm
9. http://drrajivdesaimd.com/wp-content/uploads/2013/06/dopamine-pathways.jpg
10. http://www.stats.ox.ac.uk/~hamer/images/complex.png
11. http://www.posturologiaclinica.net/img/rx_cranio_brain_02.jpg
12. http://www.nature.com/nrm/journal/v8/n8/images/nrm2208-f1.jpg
13. http://transforming-science.com/wp-content/uploads/2013/12/Zebrafish-aquarium.-010.jpg
14. http://kimgen677s10.weebly.com/uploads/3/6/1/8/3618941/290277.jpg?325
15. http://upload.wikimedia.org/wikipedia/en/thumb/c/c8/Microarray-schema.jpg/220px-Microarray-schema.jpg
16. https://denisezannino.files.wordpress.com/2013/07/zebrafish-kimmel.jpg
17. http://cdn.superbwallpapers.com/wallpapers/3d/mechanism-15796-1920x1200.jpg

1. Torres RJ and Puig JG. (2007). Hypoxanthine-guanine phosophoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome. *Orphanet Journal of Rare Diseases, 2,* 48. doi:10.1186/1750-1172-2-48
2. Torres RJ, Mateos FA, Molano J, Gathoff BS, O'Neill JP, Gundel RM, Trombley L, Puig JG. (2000). Molecular basis of hypoxanthine-guanine phosphoribosyltransferase deficiency in thirteen Spanish families. *Hum Mutat,15,* 383.
3. Jinnah HA, De Gregorio L, Harris JC, Nyhan WL, O'Neill JP. (2000). The spectrum of inherited mutations causing HPRT deficiency: 75 new cases and a review of 196 previously reported cases. *Mutat Res, 463,* 309-326.
4. Breese GR, Criswell HE, Duncan GE, Mueller RA. (1990). A dopamine deficiency model of Lesch-Nyhan disease – the neonatal-6-OHDA-lesioned rat. *Brain Res Bull, 25,* 477-484. DOI: 10.1016/0361-9230(90)90240-Z
5. Ernst M, Zametkin AJ, Matochik JA, Pascualvaca D, Jons PH, Hardy C, Hankerson JG, Doudet DJ, Cohen RM. (1996). Presynaptic dopaminergic deficits in Lesch-Nyhan disease. *New Engl. J Med, 334*, 1568-1572. DOI: 10.1056/NEJM199606133342403
6. "Lesch-Nyhan syndrome". Genetics Home Reference. US National Library of Medicine, Feb. 2013. Web. 24 Jan. 2015.
7. "Lesch-Nyhan Syndrome". NYU Langone Medical Center. Aug. 2014. Web. 25 Jan. 2015.
8. "Gout". Mayo Clinic. 25 Nov. 2014. Web. 24 Jan. 2015.
9. García PJ, Torres JR, Mateos F, Ramos T, Arcas J, Buño A, O'Neill P. (2001). The spectrum of Hypoxanthine-Guanine Phosphoribosyltransferase (HPRT) deficiency. Clinical experience based on 22 patients from 18 Spanish families. *Medicine (Balt), 80*, 102-112.
10. "Dystonias Fact Sheet". National Institute of Neurological Disorders and Stroke. 12 Nov. 2014 Web. 24 Jan. 2015.
11. Schretlen DJ, Harris JC, Park KS, Jinnah HA, del Pozo NO. (2001). Neurocognitive functioning in Lesch-Nyhan disease and partial hypoxanthine-guanine phosphoribosyltransferase deficiency. *J Int Neuropsychol Soc, 7,* 805-812.
12. Anderson LT, Ernst M. (1994). Self-injury in Lesch-Nyhan disease. *J Autism Dev Disord, 24*, 67-81.
13. Davidson BL, Tarle SA, Palella TD, Kelley WN. (1989). Molecular basis of hypoxanthine-guanine phosphoribosyltransferase deficiency in ten subjects determined by direct sequencing of amplified transcripts. *J Clin Invest, 84,* 342-346.
14. Olson L, Houlihan D. (2000). A review of behavioral treatments used for Lesch-Nyhan syndrome. *Behav Modif, 24,* 202-222.
15. Gene Ontology Consortium. An Introduction to the Gene Ontology. Accessed 26 February 2015.
16. Herron, J.C. and Freeman S. (2014). Evolutionary Analysis: Fifth Edition. Glenview, IL: Pearson Education, Inc.
17. Delsuc F, Brinkmann H, Philippe H. (2005). Phylogenomics and the reconstruction of the tree of life. *Nat Rev Genet 6*:361-375.
18. About BLAST http://www.ncbi.nlm.nih.gov/books/NBK1734/
19. Gingras AC, Gstaiger M, Raught B, and Aebersold R. (2007). Analysis of protein complexes using mass spectrometry. *Nat Rev Mol Cell Biol, 19*(4), 645-654.