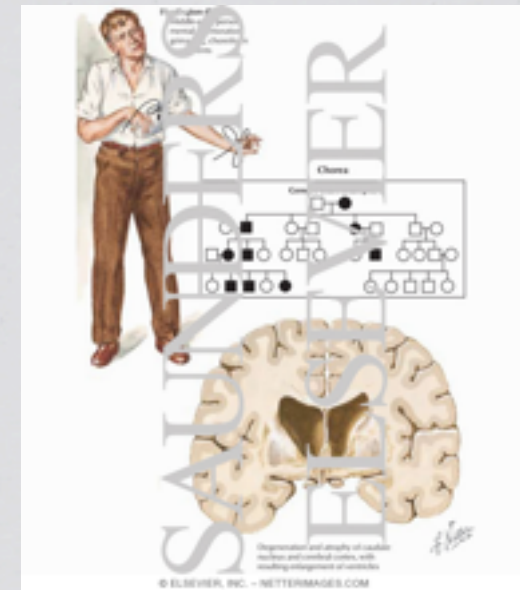
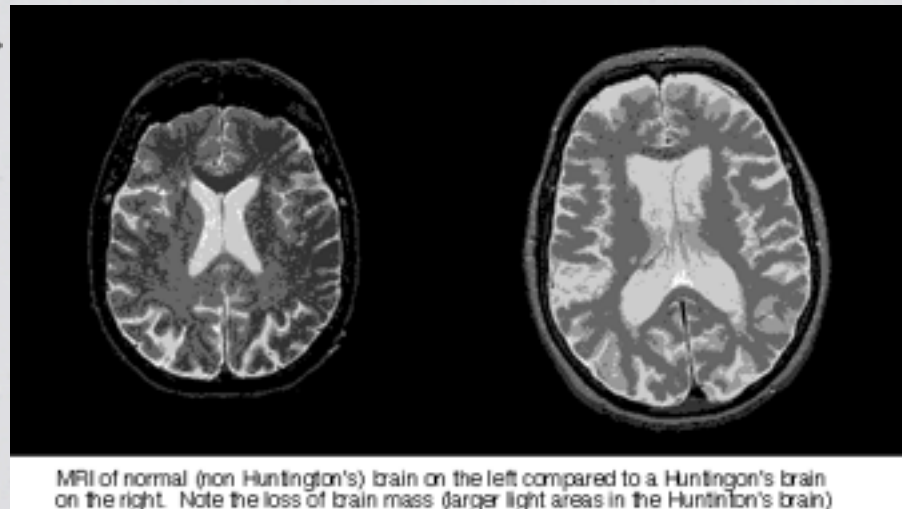

When the Huntingtin (HTT) Gene Mutates: Huntington's Disease

Afshin Khan
Stuyvesant High School

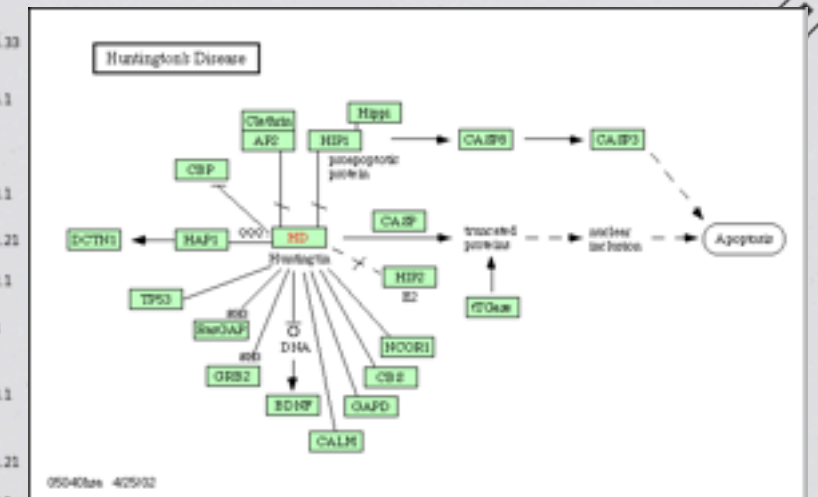
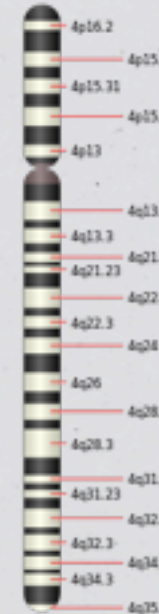
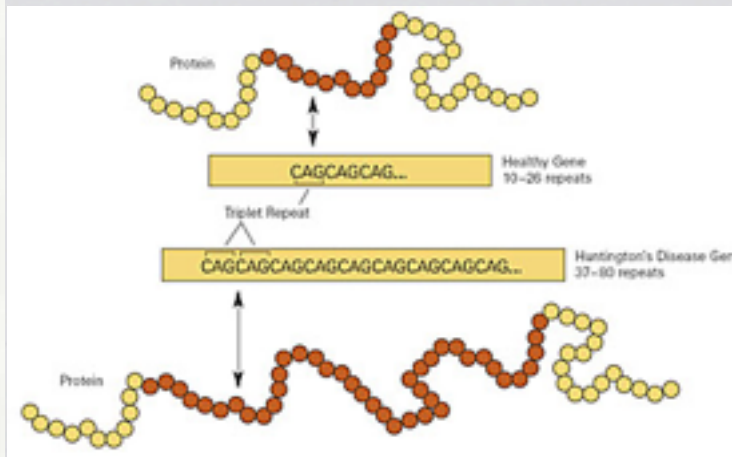
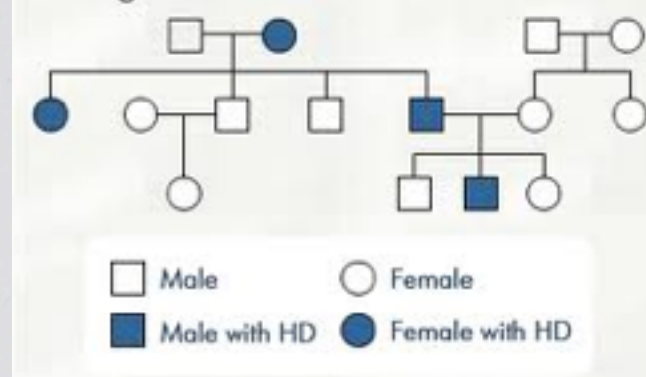
Physiology



- * Has an occurrence of 1:15,000 across the globe
- * Also known as Huntington's Chorea
- * Disease targets entire nervous system: the brain does not function normally because brain cells are not protected from toxic chemicals post-mutation
- * Onset may be early or late: eventually the person dies
- * Muscle spasms, involuntary muscle contracting, etc.
- * Difficulty speaking, swallowing, and planning, etc.

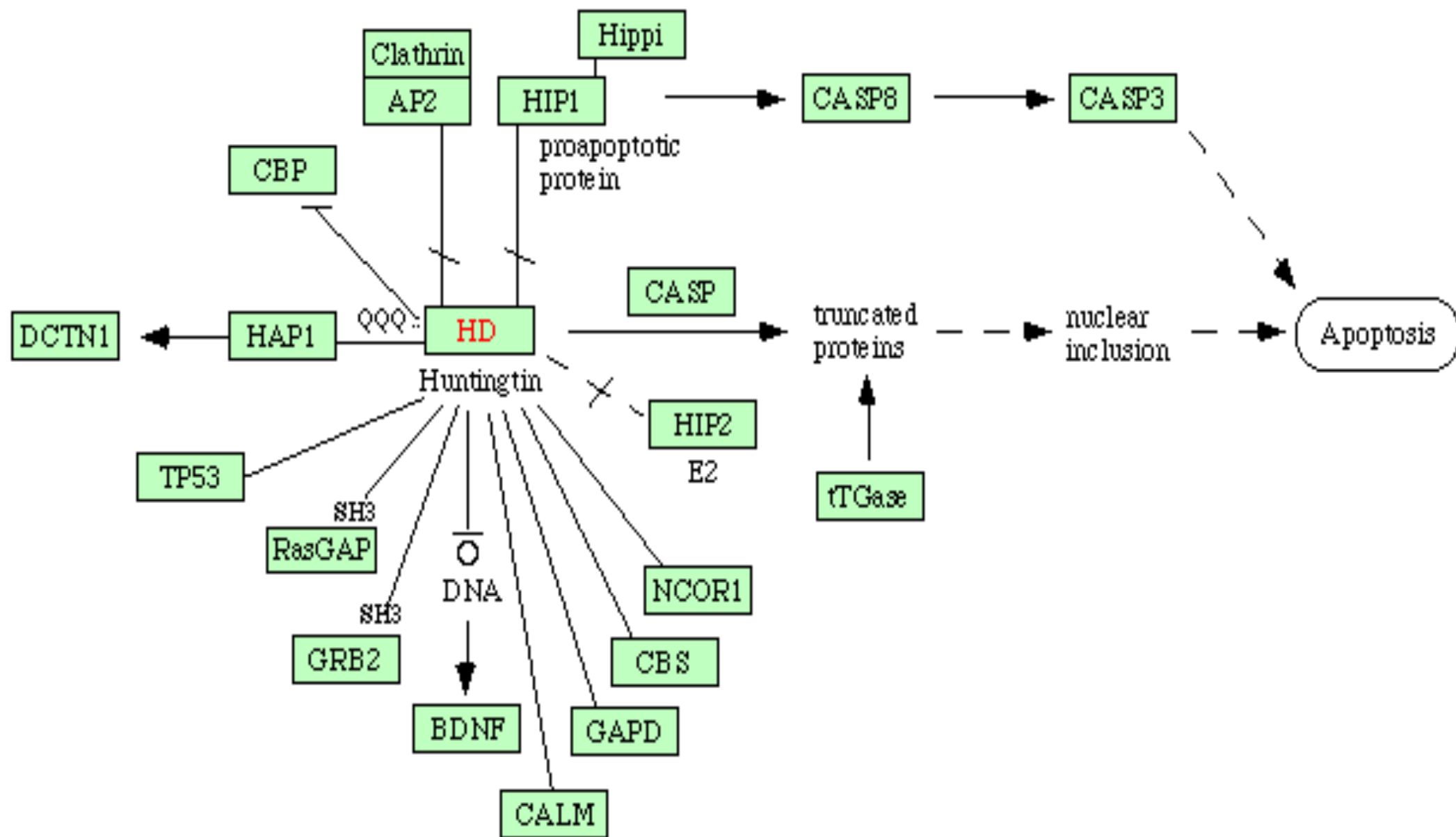
Molecular Cause

Huntington's Disease Passed On Through Generations



- * Disease is found on Chromosome 4, location 16.3
- * Function of HTT gene is not clear, a knockout of the gene in mice is lethal
- * Transmission: Autosomal Dominant, unlike other diseases of this transmission pattern, one defective copy of the gene results in equally bad symptoms as having two copies of the defective gene
- * Normal number of CAG triplets in humans is 6 to 35; number found in humans with Huntington's Disease is 36 to 39
- * This runaway mutation destroys mitochondria and brain cells

Huntington's Disease



05040hsa 4/25/02

Treatments/Risks and Limitations

- * There must be a diagnosis before any treatment takes place. This can be done using MRIs, PETs, or a CT head scan. If there is a history of the disease in the family, it is strongly encouraged to be genetically tested.
- * The disease must be dealt with genetic counseling as well.
- * Several treatments exist for Huntington's Disease, however there is no cure
- * The use of several medicines such as Tetrabenazine, Diazepam, and Depakene can work together to treat movement disorders, anxiety disorders, and migraines respectively. However, this drug "cocktail" can lead to liver damage, and possibly become a fatal combination.
- * A treatment on the horizon is the use of electrodes inserted into the brain along with a slight charge passed through the brain. This treatment can temporarily treat the patient of involuntary muscle movements and spasms. However, the limitation of this treatment is that this dose of electricity leads to short-term memory loss and difficulty learning new material.

Proposal Cure and Limitations

Scientists have cured mice (*mus musculus*) of Huntington's Disease with the drug for Alzheimer's called "Memantine."

- * *Mus musculus* HTT gene is 95% similar to *Homo sapiens* HTT
- * Using this drug and a synthetic nucleic acid named Antisense Oligonucleotide (ASO) should be suitable for a cure to Huntington's Disease.
- * This nucleic acid's base pairs are complementary to the target gene's mRNA. They pair and bind with the mRNA and break it down with an enzyme called RNase-H. The molecular instructions for the Huntingtin Protein are not translated therefore no protein is made.
- * ASOs pertain to the single-stranded RNA which is why ASOs can penetrate the cell membrane. For this reason, ASOs can be made into drugs. However, this is where the problem lies. There is no way to get the ASO into the brain directly. Therefore, the best way to get the ASO to the brain, is to pump it through the cerebrospinal fluid.
- * The most significant research study relating to this treatment was when Dr. Donald Cleveland and his research team cured several mice of Huntington's Disease using the ASO treatment.
- * The clinical trial for this treatment is now at 18 months. There remains hope for people with Huntington's Disease yet.

References

*Content

1. Rosenblatt A, et al. A physician's guide to the management of Huntington's disease. Huntington's Disease Society of America. <http://www.hdsa.org/images/content/1/1/11682.pdf>. Accessed March 28, 2011.
2. Novak MJ, et al. Huntington's disease. British Medical Journal 2010;340:c3109.
3. Depression. The Merck Manuals: The Merck Manual for Healthcare Professionals. <http://www.merckmanuals.com/home/sec07/ch101/ch101b.html>. Accessed April 4, 2011.
4. Nance M. The juvenile HD handbook: A guide for families. Huntington's Disease Society of America. <http://www.hdsa.org/images/content/1/1/11702.pdf>. Accessed March 28, 2011.
5. Paulsen JS, et al. Critical periods of suicide risk in Huntington's disease. The American Journal of Psychiatry 2005;162:725.
6. Frank S, et al. Advances in the pharmacological management of Huntington's disease. Drugs 2010;70:561.

*Images

2. Huntington's disease: Hope through research. National Institute of Neurological Disorders and Stroke. <http://www.ninds.nih.gov/disorders/huntington/huntington.htm>. Accessed March 24, 2011.
3. Suchowersky O. Huntington disease: Management. <http://www.uptodate.com/home/index.html>. Accessed April 4, 2011.
4. Katon W, et al. Initial treatment of depression in adults. <http://www.uptodate.com/home/index.html>. Accessed April 4, 2011.
5. Tost H, Wendt CS, Schmitt A, Heinz A, Braus DF. Huntington's disease: phenomenological diversity of a neuropsychiatric condition that challenges traditional concepts in neurology and psychiatry. Am J Psychiatry. 2004 Jan;161(1):28-34. PubMed citation
6. Walker FO. Huntington's disease. Lancet. 2007 Jan 20;369(9557):218-28. Review.PubMed citation
7. Young AB. Huntingtin in health and disease. J Clin Invest. 2003 Feb;111(3):299-302. Review.PubMed citation
8. Imarisio S, Carmichael J, Korolchuk V, Chen CW, Saiki S, Rose C, Krishna G, Davies JE, Tofsi E, Underwood BR, Rubinsztein DC. Huntington's disease: from pathology and genetics to potential therapies. Biochem J. 2008 Jun 1;412(2):191-209. doi: 10.1042/BJ20071619. Review.PubMed citation