Gene silencing ameliorates disease manifestations in a mouse model of Huntington's disease

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Gene silencing for Huntington’s Disease

- Mutant HD Gene
- Huntingtin Messenger RNA
- Mutant Huntingtin Protein

GENE SILENCING THERAPY

Disease
Viruses are Tools for Gene Silencing

- Genetic material for silencing
- Package into virus for transfer
- Inject into proper region of brain
The Mouse as a Model for Human Disease

• Striking similarity to humans in anatomy, physiology, and genetics

• Cost-effective and efficient tool to speed research and development of drug therapies

• Can manipulate the mouse genome to model diseases for which the causative gene is known
Preclinical Testing of Gene Silencing in an HD Mouse

- Inject virus
- Measure performance
- Collect brain tissue
- Measure gene expression
Viral-Mediated Gene Silencing Improves Motor Deficits and Depressive Behavior in HD mice

Rota Rod
4 Months Old

improved motor function

Porssolt Swim Test
5 Months Old

improved depressive behavior
Viral-Mediated Gene Silencing Reduces Mutant Htt Levels in the Striatum of HD mice

Human Htt Protein
(Normalized to β-tubulin)

AAV-Null  AAV-Htt

Reduced Htt Expression

Viral Expression in Striatum
The Road Ahead for Gene Silencing Treatment for HD

Main Conclusion from Mouse Studies:
AAV-RNAi reduces Htt levels in the brain and improves disease symptoms in the YAC128 model of HD.

ISSUES TO SOLVE:

- Safety
  - Off-targets
  - Silencing mutant and normal Huntingtin
- Delivery
  - Optimal coverage
Presenter Disclosures

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Huntington’s Disease Society of America