CHCHD10-pathy: A Recently Discovered Mitochondrial Disease with Highly Heterogeneous Manifestations

June 27

Tuesday, 12:30 pm

Billings Building—Rosedale Room

SPEAKER:

Giovanni Manfredi, M.D., Ph.D.

Finbar and Marianne Kenny Professor in Clinical and Research Neurology

Feil Family Brain and Mind Research Institute

Director, Graduate Program of Neuroscience

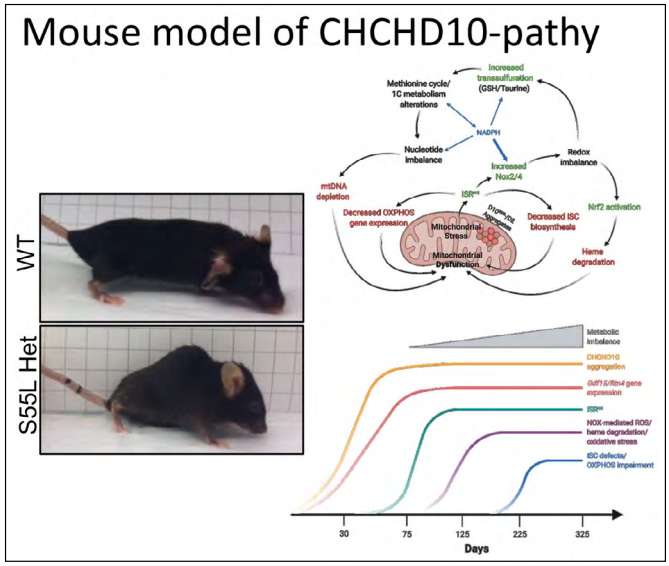
Weill Cornell Medicine

Host: Gary E. Gibson, Ph.D.

For more information contact
Darlene White
daw9085@med.cornell.edu

Abstract

Coiled-helix-coiled-helix domain containing protein 10 (CHCHD10) is the first mitochondrial protein to be associated with amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Although the normal function of D10 remains unknown, numerous pathogenic CHCHD10 mutations have been reported and associated with a wide variety of clinical manifestations ranging from neurological to cardiac diseases. Most mutations have been associated with ALS, FTD, and myopathy, including the S59L mutation, which was the first one to be identified and the most studied to date. To investigate the pathogenic mechanisms of these mutations in vivo, we have generated KO and knock in (KI) mouse models. Mutant S55L (mouse equivalent of human S59L) CHCHD10 KI mice develop protein aggregation in multiple tissues, resulting in proteotoxicity that leads to neurological defects, myopathy, and fatal cardiomyopathy. However, despite the availability of CHCHD10 mouse models, gaps in knowledge remain on the normal function of CHCHD10 (and its paralog protein CHCHD2) and on how mutations affect CHCHD10 protein structure, aggregation, metabolism, and neuronal degeneration in D10 frontotemporal dementia. This presentation will present recent, mostly unpublished findings on the putative functions of CHCHD10, pathogenic mechanisms underlying CHCHD10-pathy, and therapeutic approaches under development.



Publications

Nguyen MK, McAvoy K, Liao SC, Doric Z, Lo I, Li H, Manfredi G, Nakamura K. *Mouse midbrain dopaminergic neurons survive loss of the PD-associated mitochondrial protein CHCHD2.* Hum Mol Genet. 2022 May 4;31(9):1500-1518. doi: 10.1093/hmg/ddab329. PubMed PMID: 34791217; PubMed Central PMCID: PMC9071413.

Sayles NM, Southwell N, McAvoy K, Kim K, Pesini A, Anderson CJ, Quinzii C, Cloonan S, Kawamata H, Manfredi G. *Mutant CHCHD10 causes an extensive metabolic rewiring that precedes OXPHOS dysfunction in a murine model of mitochondrial cardiomyopathy.* Cell Rep. 2022 Mar 8;38(10):110475. doi: 10.1016/j.celrep.2022.110475. PubMed PMID: 35263592; PubMed Central PMCID: PMC9013208.

Anderson CJ, Bredvik K, Burstein SR, Davis C, Meadows SM, Dash J, Case L, Milner TA, Kawamata H, Zuberi A, Piersigilli A, Lutz C, Manfredi G. *ALS/FTD mutant CHCHD10 mice reveal a tissue-specific toxic gain-of-function and mitochondrial stress response.* Acta Neuropathol. 2019 Jul;138(1):103-121. doi: 10.1007/s00401-019-01989-y. Epub 2019 Mar 14. PubMed PMID: 30877432; PubMed Central PMCID: PMC6571048.

Burke Neurological Institute
Academic Affiliate of Weill Cornell Medicine
785 Mamaroneck Avenue, White Plains, NY 10605
burke.weill.cornell.edu/events

Burke Neurological Institute
The Science Hope Demands

Weill Cornell Medicine