Title: Progressive Myoclonus Epilepsy, Lafora Type *GeneReview*
Authors: Jansen AC, Andermann E
Updated: November 2011

Animal Models of Lafora Disease

The *Epm2a* knockout mouse model of Lafora disease. A mouse model using the knockout approach was generated by deleting the exon containing the PTP domain [Ganesh et al 2002]. Homozygous null mutants were viable and showed Lafora bodies and signs of neurodegeneration as early as age two months. Only at age four months did the knockout mice begin to display an impaired behavioral response, followed at a later stage by myoclonic seizures, ataxia, and epileptiform activity on EEG. Generalized seizures did not occur. These findings illustrate that the accumulation of Lafora bodies precedes the onset of phenotypic abnormalities.

The transgenic mouse model of Lafora disease. A transgenic mouse model of LD was generated by overexpressing laforin carrying a phosphatase inactivating point mutation (p.Cys266Ser) [Chan et al 2004]. This resulted in trapping laforin's normal yet unknown substrate and in the production of Lafora bodies in neurons, hepatocytes, and myocytes. The findings from this model regarding the localization of the laforin protein contributed significantly to the understanding of the physiologic role that laforin plays in LD. In brain, laforin resides in the neuronal somas and dendrites, similar to human disease. It localizes at the endoplasmic reticulum, but not directly on ribosomes. The model also showed that laforin preferentially binds polyglucosans in vivo and starch in vitro. Laforin is thus designed to detect polyglucosans and likely serves to initiate mechanisms to prevent their further accumulation or mechanisms to promote their removal [Chan et al 2004].

Canine model of Lafora disease. Approximately 5% of miniature wirehaired dachshunds (MWHD) in the UK exhibit LD [Lohi et al 2005]. The phenotype and the pathology observed in this breed of dog precisely replicates the symptoms observed in human LD, except for the later age of onset in dogs (age six years in dogs, equivalent to age ~40-45 years in humans). The genetic basis of LD in the MWHD consists of a coding dodecamer expansion mutation of the dog ortholog of *NHLRC1*. This mutation represents the first tandem repeat expansion mutation in any nonhuman species [Lohi et al 2005].

References

Chan EM, Ackerley CA, Lohi H, Ianzano L, Cortez MA, Shannon P, Scherer SW, Minassian BA. Laforin preferentially binds the neurotoxic starch-like polyglucosans, which form in its absence in progressive myoclonus epilepsy. Hum Mol Genet. 2004; 13:1117-29.

Ganesh S, Delgado-Escueta AV, Sakamoto T, Avila MR, Machado-Salas J, Hoshii Y, Akagi T, Gomi H, Suzuki T, Amano K, Agarwala KL, Hasegawa Y, Bai DS, Ishihara T, Hashikawa T, Itohara S, Cornford EM, Niki H, Yamakawa K. Targeted disruption of the Epm2a gene causes formation of Lafora inclusion

bodies, neurodegeneration, ataxia, myoclonus epilepsy and impaired behavioral response in mice. Hum Mol Genet. 2002a; 11:1251-62.

Lohi H, Young EJ, Fitzmaurice SN, Rusbridge C, Chan EM, Vervoort M, Turnbull J, Zhao XC, Ianzano L, Paterson AD, Sutter NB, Ostrander EA, Andre C, Shelton GD, Ackerley CA, Scherer SW, Minassian BA. Expanded repeat in canine epilepsy. Science. 2005; 307:81.