

**Study the role of patient-specific mutations by genetic disease modeling.  
From gene to function; A study to understand muscles**

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska Akademin,  
Göteborgs universitet, kommer att offentligen försvaras i hörsal Arvid Carlsson,  
Academicum, Medicinargatan 3, Göteborg.

Fredagen den 22 Mars 2019, kl 13:00

Av

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Avhandlingen baseras på följande arbeten:

- I. **Halvarsson D.M.**, Pokrzywa M., Rauthan M., Pilon M., Tajsharghi H. Myosin Storage Myopathy in *C. elegans* and Human Cultured Muscle Cells. PLoS One, 2017 Jan 26;12(1):e0170613.
- II. Kariminejad A., **Halvarsson D.M.**, Ravenscroft G., Afroozan F., Keshavarz E., Goullée H., Davis M.R., Faraji Zonooz M., Najmabadi H., Laing N.G., Tajsharghi H. TOR1A variants cause severe arthrogyriposis with developmental delay, strabismus and tremor. Journal of Brain, 2017 Sep 23; 140 (11): doi: 10.1093/brain/awx230
- III. **Halvarsson D.M.**, Olivé M., Pokrzywa M., Ejeskär K., Palmer R.H., Uv A.E., Tajsharghi H. *Drosophila* model of myosin myopathy rescued by overexpression of a TRIM-protein family member. PNAS, 2018 Jul 10;115(28) doi: 10.1073/pnas.1800727115
- IV. **Halvarsson D.M.**, Olivé M., Pokrzywa M., Norum M., Ejeskär K., Palmer R.H., Uv A.E., Tajsharghi H. *Drosophila* model of myosin storage myopathy rescued by overexpression of a TRIM-protein family member. Submitted Manuscript, Feb 2019
- V. Emrahi L., **Halvarsson D.M.**, Moselmi A.R., Hesse C, Goullée H., Laing G.N., Tajsharghi H. UNC45B, a co-chaperone required for proper folding and accumulation of myosin, as a novel gene associated with hypertrophic cardiomyopathy. Manuscript



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ABSTRACT

Many genetic diseases inherited in a dominant fashion have a complex pathological pattern. *TOR1A* mediated Dystonia-1 (DYT1) is an example of incomplete penetrance, affecting only a third of the carriers. DYT1 is an early-onset neurological disease affecting dopamine release from substantia nigra to the striatum in the brain, causing muscle tremors in muscles. We have identified the first cases of homozygous *TOR1A* mutation together with a new *TOR1A* mutation all of them showing DYT1 symptoms from birth.

The main part of this thesis has gone to describing the skeletal myosin myopathies Laing early-onset myopathy (MPD1) and myosin storage myopathy (MSM). The diseases are known for causing slow progressive muscle atrophy with huge variations on progression rate. Individuals within the same family can exhibit wildly different speed of atrophy. We show with cell assays that various *MYH7*, which all leads to myosin storage myopathy, are caused by different mechanisms. We also show that *Drosophila melanogaster*, fruit flies, carrying MPD1 and MSM mutations becomes resilient when overexpressing the enzymatic ubiquitin E3-ligase TRIM32. The enzyme is a homolog to the human MuRF enzyme, known to mediate myosin breakdown.

Lastly we have found a family where a mutation in the gene coding for myosin folding chaperone UNC-45B drives the heart condition hypertrophic cardiomyopathy. UNC-45B have been shown to be important for embryonic heart development but never been found to be associated with any muscle disease before.

**Keywords:** Muscles, Myosin, MYH7, Myosin storage myopathy, Laing early-onset myopathy, *Drosophila*, TOR1A, DYT1, HCM, heart disease

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