Predicting loss of ambulation in *FKRP*-related LGMD

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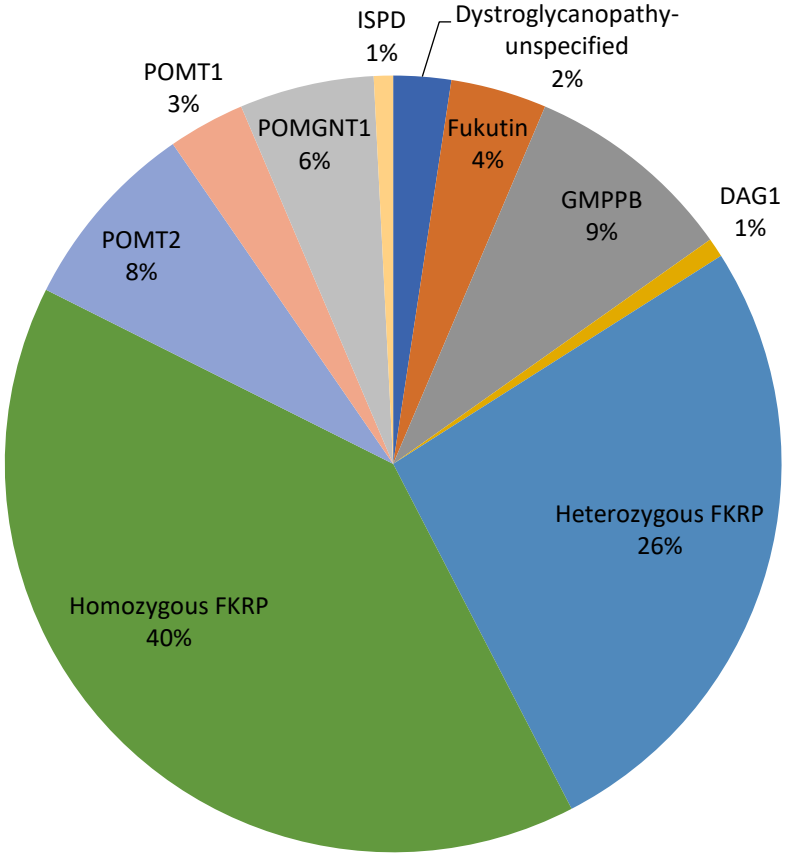
Overview

- Loss of ambulation (losing ability to walk) is one of the most important clinical landmarks during disease progression of muscular dystrophy
- Difficult to accurately predict when patients will become wheelchair bound

Wellstone Natural History Study

- Project includes all dystroglycanopathies
- For this analysis, focused on pts with most commonly affected gene *FKRP*
- Standardized motor function tests carried out annually by PTs trained in clinical trial outcome measures
  - Includes tests such as 4 stair climb (4SC), 10-meter walk time test (10MWT), and time lying to standing (TLTS)



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FKRP: Fukutin-Related Protein

- Common founder mutation: c.826C>A
- Homozygous (2 copies of c.826C>A mutation): on average milder disease with slower progression of symptoms
- Heterozygous (1 copy of c.826C>A mutation + 1 different mutation): on average more severe disease with faster progression of symptoms
- Homozygous for other mutations: variable disease progression

Loss of ambulation

- 33.7% of patients lost ambulation, the majority of whom were not homozygous for the c.826C>A founder mutation

	# of patients (%)	# of patients who lost ambulation (%)
Cohort	86	29 (33.7%)
c.826C>A homozygotes	48 (55.8%)	12 (25%)
All other genotypes	38 (44.2%)	17 (42.1%)

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50% of all participants lost ambulation by **45.6 years old**

- No difference in age at loss of ambulation between male and female patients

	# of patients (%)	# of patients who lost ambulation (%)	Range of years of disease duration between first symptom presenting and LOA (median)
Cohort	86	29 (33.7%)	5 – 60 (20)
c.826C>A homozygotes	48 (55.8%)	12 (25%)	12 – 60 (31.5)
All other genotypes	38 (44.2%)	17 (42.1%)	5 – 46 (15)

LOA = Loss of ambulation

Age range at loss of ambulation

	2 copies c.826C>A	All other mutations
Youngest to lose ambulation	31 years old	9 years old
Oldest to lose ambulation	74 years old	54 years old
Oldest still walking at last follow-up	74 years old	71 years old

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Predicting loss of ambulation with motor function tests

- 4SC, 10MWT, and time lying to standing significantly predictive of LOA

Motor function test result	# of patients	# of patients who lost ambulation (%)	median years to LOA (95% CI)
Unable to rise from floor on TLTS	29	13 (44.8%)	5.9 (2.8-8.6)
10MWT between 7-10 seconds	21	7 (33.3%)	8.6 (5.0-8.6)
4SC between 4-6 seconds	23	7 (30.4%)	9.5 (3.9-9.5)

LOA = loss of ambulation; TLTS = time lying to standing test; 4SC = 4-stair climb test time; 10MWT = 10-meter walk test time

Discussion

- Important to consider specific genotype when predicting clinical course
  - Patients with 0-1 copies of founder mutation could potentially lose ambulation in childhood
  - Patients with 2 copies of founder mutation likely to retain ambulation well into adulthood
- Standard motor function test results could be useful for predicting disease progression

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