A multicenter collaborative study on infantile onset facioscapulohumeral muscular dystrophy

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Infantile onset of FSHD

- Facial weakness <5 yrs and shoulder girdle weakness <10 yrs (Brouwer et al, 1994)
- Retinal vasculopathy
- Sensorineural hearing loss
- Epilepsy
- Metal retardation

Study objectives

1. Establish a standardized muscle testing protocol including both manual and quantitative muscle testing as well as function testing for use in children and adults with infantile onset FSHD

2. Describe the clinical phenotypes of infantile FSHD

3. Evaluate the impact of physical impairment, secondary health conditions, activity limitations and disability caused by FSHD on health-related quality of life and disability across different age groups; as well as to evaluate the utility of the FSHD clinical severity scale

Study objectives

4. Investigate for potential genetic modifiers of clinical phenotypes and disease progression in infantile FSHD. The correlation between gene expression and disease severity will be evaluated.

5. Identify biomarker candidates for infantile FSHD for evaluations of therapeutic efficacy in future clinical studies.

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The Cooperative International Neuromuscular Research Group (CINRG)

www.cinrgresearch.org

CINRG

- Founded in 1999 at Children's National Health System
- Multi-disciplinary and cross-institutional network of clinicians and scientists wishing to positively impact the lives of patients with neuromuscular disorders via research studies
- Study the cause(s), pathogenesis and clinical outcomes of neuromuscular disorders and conduct well-controlled clinical studies

CINRG Coordinating Center

- Housed within the Center for Genetic Medicine Research at Children's National Medical Center with elements spread over a selected group of centers

- Directors:
  - Coordinating Center: Dr. Avital Cnaan
  - Medical: Dr. Paula Clemens
  - Scientific: Dr. Eric Hoffman

CINRG Completed Studies

Study Title	Study Chair	Sponsor	Publications
CQMS Reliability Studies	D. Escolar J. Mayhew	N/A	Muscle and Nerve (2001) 24:787-93 and Muscle and Nerve (2007) 35:36-42
Open-Label Pilot Study of Oxatomide in Steroid-Naive DMD	G. Buyse D. Escolar	AFM MDA	European Journal of Pediatric Neurology (2007) 11:337 – 340
Open-Label Pilot Study of Coenzyme Q10 in Steroid-Treated DMD	D. Escolar	MDA	Muscle and Nerve (2011) 44:174-178
Double Blind RTC to Assess the Efficacy and Safety of Glutamine and Creatine in DMD	D. Escolar	MDA	Annals of Neurology (2005) 58:151–155
Open-Label Pilot Study of Pentoxifylline in Steroid-Naïve DMD	D. Escolar	MDA	Muscle and Nerve (2011) 44:170-173
Double Blind RTC of Daily Pentoxifylline as Rescue Treatment in DMD	D. Escolar	FED	Neurology (2012) 78;904-913
Double Blind RTC of Daily vs. High Dose Weekly Prednisone in DMD	D. Escolar P. Clemens	MDA	Neurology (2011) 77:444-452
Comparative Study of Clinical Endpoint: HHM vs. CQMS	T. Duong	MDA	Manuscript in preparation
Evaluation of LGMD	S. Sparks	MDA	Manuscript in preparation
Cardiac Outcome Measures in Children with Muscular Dystrophy	P. Clemens	NIH	Manuscript in preparation

CINRG Clinical Research Network
27 SITES

Disease Census

- Duchenne:
  ~ 3,000 pts
- Becker:
  ~ 600 pts
- FSHD:
  ~ 500 pts
- LGMD:
  ~ 320 pts
  known type
  ~ 600 pts
  unknown type

All centers are major neuromuscular referral centers

CINRG Clinical Site Locations

US Sites

- Children's National Medical Center, Washington, DC
- Children's Hospital, Richmond, VA
- University of Pittsburgh, Pittsburgh, PA
- University of Tennessee, Memphis, TN
- University of Puerto Rico, San Juan, PR
- Washington University - St. Louis, MO
- Mayo Clinic, Rochester, MN
- University of California - Davis, Sacramento, CA
- Texas Children's Hospital, Houston, TX
- University of Minnesota, Minneapolis, MN
- Carolinas Medical Center, Charlotte, NC
- Ann and Robert H. Lurie Children's Hospital of Chicago,Chicago, IL
- Duke Medical Center, Durham, NC
- University of Florida, Gainesville, FL

International Sites

- Hadassah, Hebrew University Hospital, Jerusalem, Israel
- Holland Bloorview Kids Rehab, Toronto, Canada
- Apollo Hospitals, Chennai, India
- Royal Children's Hospital, Melbourne, Australia
- Fundacion Favaloro, Buenos Aires, Argentina
- Queen Silvia Children's, Göteborg, Sweden
- Children's Hospital at Westmead, Sydney, Australia
- Alberta Children's Hospital, Calgary, Canada
- University of Alberta, Edmonton, Canada
- Centro Clinico NeMO Hospital, Milan, Italy
- National Center of Neurology and Psychiatry, Tokyo, Japan
- Kobe University, Kobe, Japan
- Newcastle University, Newcastle upon Tyne, UK

CINRG Site Personnel

Each site team has the following minimum staff:

- Site Principal Investigator
- Clinical Research Coordinator
  - Coordinate study visits
- Two Physical Therapists
  - Trained and certified as Clinical Evaluators for CINRG
  - Performs CQMS tests

CINRG Quantitative Measurement System (CQMS)

- Over 50 physical therapists certified through reliability training on commonly used clinical trial endpoints in NMD
- Harmonization of outcomes
- Standardization of equipment

Study Design/Enrollment

- Recruit 50 participants with infantile onset FSHD across all centers
- Average enrollment is 3 participants per site but we encourage sites to enroll to their maximum capability
- Complete enrollment within a 12 months period (estimated enrollment closure Winter 2014)

Inclusion Criteria

The presence of all of the following features based on review of medical records and/or direct examination:

- Onset of symptoms involving the facial or shoulder girdle muscles at or younger than10yr, **and**
- Autosomal dominant inheritance in familial cases, **and**
- Contraction of the D4Z4 repeat array from 1–10 (10 – 38 kb) copies in the 4q35 subtelomeric region, based on established molecular genetic techniques

Exclusion Criteria

- Symptomatic cardiomyopathy or severe cardiac arrhythmia which may limit the ability to complete the study protocol
- Maternal mode of inheritance (also referred to as mitochondrial inheritance)
- Evidence of an alternative diagnosis based on muscle biopsy or other available investigations
- In the Investigator's opinion an inability to comply with the protocol

Study Assessments

- Physicians Assessments (approximately 30 min)
- Cognitive assessments (approximately 30 min) – Age restrictions in areas
- Standardized Self-Administered Questionnaires (approximately 30 min)
- Clinical Evaluator Assessments (approximately 140 min) - Age restrictions in areas

Study Assessments

Sub-Specialties (Optional Based on Site Resources)

- Hearing Assessment (approximately 30 min)
- Ophthalmologic Assessment (approximately 60 min)
- Speech Assessment (approximately 30 min) - Age restrictions in areas

Optional Participant Assessment

- Blood Sample Collection (approximately 10 min)

Funding Support

- FSH Society (USA)
- Muscular Dystrophy Canada (Canada)
- FSHD Global Research Foundation (Australia)