Dysferlinopathy Registry and Natural History Study

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What are Dysferlinopathies?

- A very heterogeneous group of rare autosomal recessive inherited neuromuscular disorders
- Slowly progressive muscle wasting and weakness
- Variable severity and distribution in association with high CK levels
  - Miyoshi myopathy
  - Limb Girdle Muscular Dystrophy, type 2B (LGMD2B)
  - Proximodistal forms
  - Others, ...
- Very variable age of onset
- Mutations in the *DYSF* gene → complete or partial absence of the dysferlin protein in skeletal muscles
Dysferlinopathies: Molecular Diagnosis

- Biological analysis of the level of the dysferlin protein
- Mutational analysis of the *DYSF* gene: time and cost consuming!
  - A 230kb long gene, with 6,2kb of coding sequence spanning 55 exons
  - Large mutational spectrum (>250 ≠ pathogenic mutations)
  - No mutational hotspot

- Unknown genotype-phenotype relationship
- High intra-familial clinical heterogeneity

Why an International Registry for Dysferlinopathies?

Rare disease and challenging diagnosis
(small numbers of patients)
+ Large mutational spectrum
(potential future therapies might be restricted to patients carrying specific mutations)
= Difficulty to identify enough eligible patients for a specific study/trial
The International Dysferlinopathy Registry: Expectations

- Register patients worldwide
- Store patients’ data
  - Personal details
  - Key medical information concerning their disease
- Help researchers to understand the genotype – phenotype relationship
- Help with patient’s recruitment for:
  - Natural history studies
  - Other scientific researches with patients’ involvement
  - Clinical trials
- Support other activities to improve patients’ care (assessment / dissemination of standards of care)
- Inform patients about their condition (in close collaboration with patients’ organizations)
Our Involvement: from the UMD-DYSF Database to the International Dysferlinopathy Registry

- 2001: creation of the **UMD-DYSF** Locus-Specific Database
  - predictive tools for the pathogenicity of missense mutations
- Repository of **DYSF** disease-causing mutations
- Numerous bioinformatics analysis tools
- Freely available at the end of this year --> [www.umd.be/DYSF/](http://www.umd.be/DYSF/)
  (Martin KRAHN, Christophe BEROUD)

- 2011-early 2012:
  - development and launching of the International Dysferlinopathy Registry (IDR)

**Endorsed and funded by:**
[www.jain-foundation.org](http://www.jain-foundation.org)

- **Eligibility criteria**: genetically confirmed diagnosis (one or more pathogenic mutation)
- [300-1000] expected registrants
Organization of the International Dysferlinopathy Registry

The patient

Consultation and modification of data

Coordination of the Steering Committee

Data sharing
(if the patient has allowed the IDR to do so)

Information for the patient, relevant to him/her and his/her condition, in particular about any clinical trial or research study for which he/she might be eligible

Online registration

Completes and validates his/her Registration and Consent Questionnaire (I)

Contact details and consent

Connexion data

Medical data

E-mail to the patient with the login and password of his/her new user account

Secured connexion to his/her personal user account on the IDR website

Completes his/her Registration Medical Questionnaire (II)

Data handling

Dr. G. BLANDIN: curator

Dr. M. KRAHN: chief scientist

Dr. C. BEROUD: chief scientist for the bioinformatics development and maintenance of the registry

Data collection and data storage

The International Dysferlinopathy Registry database

Secured server

The patient’s data are anonymized with the creation of a unique sequence number specific to each patient

The International Dysferlinopathy Registry

Health professional

Clinical and genetic diagnosis, and medical follow up of the patient

Message to the health professional asking to complete the Registration Medical Questionnaire (III)

Completes the Questionnaire III and sends it back to the IDR

Medical data

Exportation of the anonymized medical data associated with the IDR-ID

Copy of part of the anonymized exported data onto the UMD-DYSF website (www.umd.be/DYSF/)

Data analyses with dedicated UMD bioinformatics tools

Third parties

Planning of research studies or clinical trials

Send a request to access specific anonymized IDR data

Upon approval, the request is processed and a data-analysis report is sent

Steering Committee

Coordination of the registry

TREAT-NMD Global Database Oversight Committee

Patients' organisation

Orchestrating a cure for dysferlinopathies

JAIN FOUNDATION

TREAT-NMD
Neuromuscular Network

Identification of potentially eligible patients within the registry patients

Information to these patients by sending them the NH study leaflet and other relevant NH study info.

Information through the registry leaflet and distribution (with the NH study leaflet) to participating centres to help recruiting patients followed by these centres.
An International
Natural History Study for Dysferlinopathies

What is the purpose of this study?

- To characterise the natural progression and pathophysiology of dysferlinopathies
- To delineate clinical outcome measures appropriate for future clinical trials
- To discover biomarkers that can be used to track disease severity and progression

Endorsed and funded by JAIN FOUNDATION (www.jain-foundation.org)

Study Coordinator Investigator: Prof. Kate Bushby
Recruitment for the Natural History Study

- **Where will this study take place?**
  - At 14 study sites in Europe, Japan, Australia and US.

- **When?**
  - A 5-years study with pre-screening starting in early 2012

- **Who will take part?**
  - ~150 patients
  - Residents in study site countries
  - Ambulant (100) and non ambulant patients (50)
  - Confirmed diagnosis of dysferlinopathy
    - Two identified disease-causing mutations
    - One identified disease-causing mutation associated with significant decrease of dysferlin protein level
  - Registration with the International Dysferlinopathy Registry
Data collection and storage

- Longitudinal data from 6 visits over 3 years
  - Medical assessments, incl. general physical & neurological examinations; medical questions; activity, quality of life & pregnancy questionnaires
  - Physiotherapy assessments, incl. muscle strength testing (manual muscle testing, myometry); functional/activity testing; Jebsen test; Activlim qu.; EK scale; timed tests
  - MRI scans and MRS measurements
  - Blood samples for laboratory tests
  - OPTIONAL (at first visit): additional blood sample and skin sample

→ Stored in an anonymous database linked to the identifying data in the International Dysferlinopathy Registry

→ Stored in a biobank, with cross-links between the samples & other data from the Natural History study
Take Home Message

The International Dysferlinopathy Registry

- Eligibility criteria: one or more identified pathogenic mutation in the *DYSF* gene.
- Registration at patients’ initiative with collaboration of their doctors.
- Online registration for the patients.
- Availability of part of patient’s anonymous medical data on www.umd.be/DYSF/, along with all UMD analysis tools.
- Patients will be informed about the Natural History study

The International Natural History study

- Eligibility criteria: one or more identified pathogenic mutation in the *DYSF* gene and registration with the International Dysferlinopathy Registry.
- Recruitment of 150 patients (ambulant and non ambulant) to participate in six medical and physio assessments visits over three years.
- Longitudinal data will be collected and linked to the patients’ identifying data in the registry.

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