16 July 2010
TREAT-NMD newsletter no. 82
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welcome

Welcome to the latest TREAT-NMD newsletter.

This week's edition includes:

- a summary of a recent meeting on clinical outcome measures in DMD

- a progress report on the NMD-Chip project

- a report on the second TACT review meeting

- an update on the translations of the DMD family guide

We would like to thank those who have contributed to this week's edition. This newsletter relies on input from our readers. If you have anything you wish to be included in the next newsletter please contact us at info@treat-nmd.eu

at a glance...

19-23 Jul 2010 12th International Congress on Neuromuscular Diseases - Naples, Italy

23-25 Jul 2010 Jennifer Trust Conference and AGM - Stratford upon Avon, UK.

30 Jul - 1 Aug 2010 The Biennial FSHD International Patient and Researcher Network Meeting - Las Vegas, Nevada, USA

13-15 Aug 2010 Empower 2010 - Myotonic Dystrophy Family Conference - Minneapolis, MN, USA

14 Aug 2010 Annual BMD Conference - Boston, MA, USA

14-15 Aug 2010 CMD Family and Affected Person Conference - Philadelphia, PA, USA,

29 Aug - 1 Sept 2010 European Meeting on Next Generation Sequencing - Leiden, Netherlands

9-10 Sept 2010 MD2010 - 4th conference for the Muscular Dystrophy Association of Western Australia - Perth, Western Australia

Clinical Outcome Measures in DMD - meeting summary

On June 28 and 29, 25 participants from Europe and the US met in Washington DC to discuss Clinical Outcome Measures in Duchenne Muscular Dystrophy in the context of clinical trial design. The meeting was organized by TREAT-NMD and the NCMRR – DC at Children's National Medical Center and supported by CureDuchenne, the Foundation to Eradicate Duchenne and Ryan's Quest.

This meeting was planned as a follow-up to the September 2009 EMA meeting where a clear directive was given that an international consensus needed to be developed to provide guidance on age appropriate clinical outcome measures for use in clinical trials for DMD, especially as these relate to clinically meaningful events. In order to establish the international dataset on which to base such decisions, in this meeting, results from 8 natural history data sets, representing over 1500 patients, were collectively examined to create a robust and contemporary picture of disease progression. The various outcome measures used in these studies were discussed to determine their sensitivity, reliability and applicability in clinical trials as well as relationship to disease progression. Other topics included new methods to analyze data, gaps in age/status of current datasets, and the need to standardize data collection. The 8 data sets presented were: CINRG DMD Natural History Study, UK North Star Project, Italian North Star Project, UDP, MFM, Danish DMD Dataset, PTC 124 trial control group data and the MD-NET cyclosporine trial dataset.

The meeting demonstrated that we have a strong foundation on which to base decisions around clinical trial design in DMD. There is no doubt that trial design in DMD is challenging given the complexity and variability of the disease progression but when all the results from the prospective and retrospective datasets is put together, much is known about the current natural history of DMD. Outcome measures are reasonably well defined making multicenter clinical trials feasible. The value of cross-collaborative efforts of clinicians, researchers, academics and advocacy together with industry cannot be overestimated in driving forward this paradigm.

A comprehensive meeting report will be published in mid-September.

Co-Chairs	Presenters	Other Participants
Kate Bushby, MD	Ted Abresch, MS	Abby Bronson, MBA
Ed Connor, MD	Leone Atkinson, MD	Avital Cnaan, PhD
	Jo Auld, MBA	Paula Clemens, MD
	Michelle Eagle, PhD	Valerie Cwik, MD
	Kevin Flanigan, MD	Tina Duong, MPT
	Julaine Florence, PhD	Peter Gilbert
	Erik Henricson, MPH	Emma Heslop, MSc
	Petra Kaufman, MD	Eric Hoffman, PhD

16-19 Sept 2010 EAMDA 40th Annual General Meeting - Milan, Italy

18 Sept 2010 Muscular Dystrophy Campaign Conference - Birmingham, UK

20-22 Sept 2010 Muscle Study Group Annual Meeting - Buffalo, NY, USA

01-02 Oct 2010 European Research Conference in Paediatric Neurology - Leuven, Belgium

12-16 Oct 2010 World Muscle Society International Congress - Kumamoto, Japan

21-22 Oct 2010 FSH Society FSHD International Research Consortium Meeting - Watertown, MA, USA

Please note: This is only a selection of upcoming meetings. To see all our listed meetings click here.

Anna Mayhew, PhD

Annie Kennedy

Craig McDonald, MD

Robert Leshner, MD

Eugenio Mercuri, MD

Allan Reha

Christine Payan, MD

Birgit Steffensen, PT, PhD

Glenn Walter, PhD

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Gene chips for the diagnosis of NMDs - an update from the NMD-chip project

NMD-chip (www.nmd-chip.eu) is a scientific project funded by the European Union. Its aim is to design, develop and validate new sensitive high-throughput DNA microarrays ("gene chips") to diagnose patients affected by inherited neuromuscular disorders (NMDs).

The project addresses two main issues facing neuromuscular genetics: diagnosis of mutations in genes already known to be involved in NMDs and discovery of new genes not previously known to be responsible for NMDs. Even though the gene responsible for the condition can be determined in around 60 to 70% of cases, the fact that many different genes may need to be tested means that obtaining a genetic diagnosis is often a lengthy and expensive process involving testing of many genes one by one until the mutation is found. Chip technology can allow all the potentially relevant genes in a patient's DNA to be tested simultaneously, which is a much faster and cheaper process. The project is designing chips for the diagnosis of mutations already known to cause Duchenne / Becker muscular dystrophies (DMD/BMD), limb girdle muscular dystrophies (LGMD), congenital muscular dystrophies (CMD), and hereditary motor-sensory neuropathies or Charcot-Marie-Tooth neuropathies (CMT). These diagnostic chips are described as "known-gene chips".

However, another problem facing doctors and patients is that not all genes responsible for neuromuscular disorders have yet been discovered, and an estimated 30 to 40% of patients are left without a diagnosis even once all relevant known genes have been tested. The NMD-chip project is therefore also developing "candidate-gene chips" to look for mutations in patients who have a neuromuscular disorder where the gene responsible has not yet been discovered.

The scientific strategy of the project is to design four types of chip: two for known genes, and two for candidate genes. In each case, both comparative genomic hybridization (CGH) arrays and sequence capture chips are being developed – the former to test for insertions and duplications and the latter for point mutations. The technology used, developed by Roche-Nimblegen, allows up to 2.1 million probes to be spotted on one chip, and the resulting images to be analyzed with a 2-micron resolution scanner. The project is making use of the new generation of 12-plex chips, each chamber comprising 72,000 probes covering all the exons, intron flanking regions, and when known, deep intronic mutation spots of known genes for each group of pathology (CMD / LGMD / DMD / CMT).

The project has now reached its half-way point, and the first-generation CGH chips for known genes have been validated. Two CGH-arrays containing probes covering all genes known to be involved in NMDs have been developed. The first array is dedicated to muscular dystrophies (including both dominant and recessive LGMDs), congenital muscular dystrophies, and congenital myopathies. The second array is dedicated to hereditary motor sensory neuropathies. These chips will now become part of the standard diagnostics workflow to progressively replace the current techniques.

Sequence capture chip design was initiated after validation of the CGH arrays, and the SC chips are in production and validation. Results for LGMD/DMD/CMD sequence selection will soon be compared to another capture technique "in solution" called Sure Select from Agilent, which it has been suggested may give better results. Both technologies will be evaluated, and the better one will be selected for the next steps of the project.

In the research part of the project, the development of the candidate-gene chips, the chips have been designed and are currently under validation. These chips aim to identify new genes involved in the three groups of diseases of the project, namely congenital muscular dystrophies (CMD), Charcot-Marie-Tooth diseases (CMT) and limb-girdle muscular dystrophies (LGMD). A list of the most likely candidate genes for CMD, CMT and LGMD was developed, and on the basis of this, CGH-arrays for the 3 groups of diseases have been designed.

A large reference materials database has also been created to collect relevant samples to be used as positive controls on the chips. From a bioinformatics point of view, several tools have been created to improve the chip design, to collect all the data, and to analyse the pathogenicity of the mutations detected by the chips.

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TACT Second Review Meeting Update

TACT update – 16th July 2010

The TREAT-NMD Advisory Committee for Therapeutics (TACT) held its second review meeting on the 5th – 6th June 2010, which brought together 18 multidisciplinary members of the committee. During the meeting the TACT members discussed three proposals submitted by an academic clinical researcher and two industrial researchers from France and the US:

1. P188 - James Symons, PhD, Phrixus Pharmaceuticals, US
2. N-Acetyl cysteine (NAC) - Ana Ferreiro, MD, Institute of Myology, France
3. Laminin-111, Bradley L Hodges, PhD, Prothelia, US

Each researcher participated in the meeting via teleconference for one hour to discuss their proposal, which provided helpful additional context for committee members as well as clarification of specific areas where the researchers were seeking specific advice. Within 6 weeks of the meeting the committee generates an assessment report providing recommendations, including specifics to strengthen the proposal and to answer questions raised by the researchers. TACT hopes that this advice will be useful in effectively planning the next stages of the projects and strengthen the proposals they may eventually submit to funding organisations.

To help inform the community, TACT will also generate a non-confidential summary report, with input from the applicants, which will be made available via the TREAT-NMD website by 30th July 2010. However, parties interested in detailed information on TACT's recommendations should request the full TACT report from the researcher.

Additionally, in response to the questions frequently asked by researchers and based on the observations made by TACT over the first two review meetings, the TACT core group have generated general recommendations and guidelines for future researchers who plan to request a TACT review. This information is available on the TREAT-NMD website www.treat-nmd.eu/about/TACT/guidance/ and links to relevant documents and resources, identified as key points to consider, are provided on the guidance page whenever possible.

Following the review meeting in Barcelona, several TACT committee members met with a number of charitable funding organisations and discussed how the educational and advisory role of TACT can further contribute to subsequent more informed, quality applications to funding organisations. It was acknowledged that although the TACT review and the application to funding organisations are two distinct processes (TACT does not provide funding) it is important to establish a mechanism to further synergize the 2 efforts and provide continuity across processes. Discussions on how this can be achieved are ongoing between TREAT-NMD and funding organizations.

The deadline for future proposal submissions for the next TACT meeting (15th-16th January 2011) is the 15th October 2010 and researchers should contact the TACT secretariat (Emma.Heslop@treat-nmd.eu) to discuss their proposal before completing the full submission form.

TACT Review Participants

TACT core group

Cristina Csimma	Virdante Pharmaceuticals, USA
Didier Caizergues	GENETHON, France.
Petra Kaufmann	NIH, USA
Rudolf Korinthenberg	University of Freiburg, Germany
John McCall	PharmMac LLC, USA
Jerry Mendell	Nationwide Children's Hospital, Ohio, USA
Kanneboyina Nagaraju	Children's National MC Washington, USA
Dominic Wells	Royal Veterinary College, London, UK

Additional TACT experts

Marita Pohlschmidt	Muscular Dystrophy Campaign, UK
Elizabeth Vroom	Duchenne Parent Project, Netherlands
Gunnar Buyse	Leuven University, Belgium
Annamaria De Luca	Università degli Studi di Bari, Italy
Michelle Eagle	Newcastle Muscle Centre, UK
Miranda Grounds	The University of Western Australia, Australia

Dieter Hauschke	University Medical Center Freiburg , Germany
Monique Ryan	The Royal Children's Hospital, Australia
Elizabeth McNeil	Food and Drug Administration, USA
Thomas Voit	Institut de Myologie, France

TACT secretariat

Kate Bushby	Newcastle University, UK
Emma Heslop	Newcastle University, UK
Volker Straub	Newcastle University, UK

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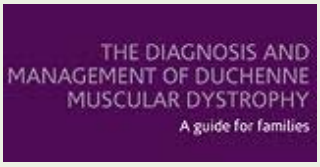
Diagnosis and Management of DMD - translations of the family guide



The Family Guide for the diagnosis and management of Duchenne Muscular Dystrophy has been enthusiastically received since its launch in late March. Ensuring that this is available in as many languages as possible is a significant step in making it accessible to all DMD patients and families. The “print friendly” version will be the most widely available, with some patient organisations also producing the printed brochures.

Bulgarian, Spanish and Romanian versions are now complete and available to download from the TREAT-NMD website, and a further sixteen translations are currently underway. In less than four months, this is excellent progress, and we wish to thank all the volunteers for offering to translate the family guide.

Further increasing the number of translations available will bring considerable benefits for DMD patients around the world. In addition, making best practice care guidelines available in multiple languages forms a major part of the recently launched CARE-NMD project. TREAT-NMD would therefore like to put a call out for volunteers to translate the family guide into languages not yet covered. If you are interested in helping with this, or are aware of other translations so that we can keep a comprehensive list of translations up to date, then please contact Karen Rafferty at TREAT-NMD.

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