Journal of Neuromuscular Diseases 8 (2021) 323–334
DOI 10.3233/JND-219001
IOS Press

Meeting Report

Report on the 5th Ottawa International Conference on Neuromuscular Disease & Biology – October 17-19, 2019, Ottawa, Canada

Jodi Warman-Chardon[a,b,c,d,e], Bernard J. Jasmin[d,e], Rashmi Kothary[a,d,e,f,g] and Robin J. Parks[a,d,f,g,*]
[a]*Department of Medicine, The Ottawa Hospital and University of Ottawa, Canada*
[b]*Department of Genetics, Children's Hospital of Eastern Ontario, Canada*
[c]*Neuroscience Program, Ottawa Hospital Research Institute, Canada*
[d]*Centre for Neuromuscular Disease, University of Ottawa, Canada*
[e]*Department of Cellular and Molecular Medicine, University of Ottawa, Canada*
[f]*Regenerative Medicine Program, Ottawa Hospital Research Institute, Canada*
[g]*Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Canada*

Pre-press 20 January 2021

INTRODUCTION

Neuromuscular diseases (NMD) include a broadly defined group of genetic and acquired disorders of the motor neuron, peripheral nerve, neuromuscular junction and skeletal muscle. Many of these disorders cause progressive functional muscle wasting and weakness, sensory loss, disability and premature death. Although likely an underestimate given the rarity of many NMD, conservative prevalence estimates are up to 90/100,000 [1–3]. Clinical implementation of the revolutionary advances in genetic diagnosis, such as next generation sequencing, have accelerated the discovery of new disease-causing genes [4] and led to the development of several therapies to treat rare genetic NMD [5]. Such progress clearly highlights that we are entering a new era of highly impactful diagnostic and therapeutic discoveries thereby providing much hope for the future of those impacted by NMD.

The rapid increase in discoveries in NMD have emerged due to increasing collaborations between basic science researchers, clinicians and patients/patient organizations. Basic researchers investigate fundamental mechanisms of disease pathogenesis in model systems and develop novel approaches to treat the underlying and/or secondary defects. As therapies can only advance so far in model systems, clinicians provide invaluable expertise in disease onset and management, as well as test new potential therapies in human clinical trials. Accordingly, the collaborative link between basic researchers and clinicians is essential to bring novel therapies into the clinic. Similarly, the role of patients and patient advocacy organizations create a forceful and necessary voice to encourage governmental organizations to support research into rare disease and approve novel therapeutics. Patient involvement is also crucial for translational studies and clinical trials to help valid the efficacy of new treatments. Clinicians, basic science researchers

*Correspondence to: Robin J. Parks, Room C4415, 501 Smyth Road, Regenerative Medicine Program, Ottawa Hospital Research Institute, Ottawa, ON, K1H 8L6, Canada. Tel.: +1 613 737 8123; Fax: +1 613 737 8803; E-mail: rparks@ohri.ca.

ISSN 2214-3599/$35.00

and patients/patient organizations must be unified, and the forged links need to remain seamless and strong to promote truly innovative NMD research and, ultimately, improve patient care and outcomes.

The 5th Ottawa International Conference on Neuromuscular Disease & Biology (Ottawa NMD 2019) was held in Ottawa, Canada, October 17-19, 2019. The aim of the conference was to bring together international NMD experts in clinical care, translational medicine and fundamental science. The speakers highlighted exciting advances in development of novel therapies, discoveries in stem cell biology and disease pathogenesis and new standards in clinical care in NMD. The Conference was organized to encourage networking and attendees were provided opportunities to engage in discussions and develop future collaborations. The conference was co-organized by Drs. Jodi Warman-Chardon (The Ottawa Hospital (TOH)/Children Hospital of Eastern Ontario, Canada), Robin Parks (Ottawa Hospital Research Institute (OHRI), Canada), Bernard Jasmin (University of Ottawa (uOttawa), Canada), and Rashmi Kothary (OHRI, Canada). Summaries of our previous Ottawa NMD conferences are also available [6–8].

CONFERENCE STRUCTURE

The Conference provided clinical and scientific sessions highlighting important clinical management approaches and research discoveries for patients with NMD. Speakers were chosen based on significant scientific contributions to the NMD field and a recognized ability to engage a broad audience at a high level, regardless of attendee stage of career and background. The Conference featured 35 internationally-recognized session speakers (10 from Canada, 16 from the United States, and 9 from Europe), and over 300 attendees including many trainees.

The Conference was divided into a keynote address and 11 sessions that were categorized by disease type (*e.g.* Amyotrophic Lateral Sclerosis (ALS), Spinal Muscular Atrophy (SMA), Myopathies, etc.). Five of the conference sessions were of broad interest and included a progression of basic science, translational medicine and clinical research approaches to specific NMD. These five sessions were attended by all conference delegates. There were an additional six 'breakout' sessions focusing on recent advances in either basic or clinical NMD research. For the two formal poster sessions, 130 abstracts were submitted for presentation and all posters were available for viewing throughout the entire Conference. Nine of the submitted abstracts were also selected for short platform presentations during the main scientific sessions. Two networking events provided excellent opportunities for social interactions between attendees.

The Conference was hosted by the University of Ottawa Dr. Eric Poulin Centre for Neuromuscular Disease (CNMD). Dr. Poulin was an illustrious surgeon, academic and leader, who assumed for several years the joint role of Chair and Chief of the Department of Surgery at the Faculty of Medicine (uOttawa) and the Ottawa Hospital. Dr. Poulin passed away too early being afflicted by ALS. A generous donation from his wife, Ms. Margo Brousseau, to the CNMD has allowed the Centre to expand considerably its efforts into ALS research while also supporting the CNMD in general. Today, the CNMD is comprised of over 60 basic scientists and clinicians/clinician researchers and over 200 graduate students, postdoctoral fellows, residents and clinical fellows in Ottawa, Canada. CNMD clinicians and researchers hold their primary appointment at either the University of Ottawa (uOttawa), The Ottawa Hospital (TOH), Ottawa Hospital Research Institute (OHRI), Children's Hospital of Eastern Ontario (CHEO), CHEO Research Institute (CHEORI) or the uOttawa Heart Institute (uOHI). All session moderators were members of CNMD.

OPENING DAY AND KEYNOTE SPEAKER

Opening remarks were provided by Drs. Jodi Warman-Chardon (TOH, CAN) and Robin Parks (OHRI, CAN), Co-Directors of CNMD, who welcomed the conference speakers and attendees to Ottawa. Dr. Rashmi Kothary (OHRI, CAN) hosted the Keynote Session. Preliminary remarks were provided by Dr. Karim Khan (University of British Columbia, CA), Scientific Director of the Institute of Musculoskeletal Health and Arthritis (IMHA) at the Canadian Institutes of Health Research (CIHR). Dr. Khan briefly discussed the framework for his position within CIHR, in part to convey the importance of research to Canadian political leaders, and to act as a champion for research areas that fall under the IMHA mandate. Dr. Kothary introduced the Keynote Speaker for the Ottawa NMD 2019 meeting, Dr. Elizabeth McNally. Dr. McNally is Ward Professor and

Director of the Center for Genetic Medicine at Northwestern University and Feinberg School of Medicine. Dr. McNally's keynote address was entitled, "Modifier signals driving therapy development in muscular dystrophies." Dr. McNally provided context for her talk by noting that patients with γ-sarcoglycan deficiency with the exact same genetic mutation can show dramatically different phenotypic presentation – some patients are affected as children, while others are still ambulatory well into adulthood. This phenotypic variation between patients is, in part, due to the presence of genetic modifiers that modulate the disease state. A similar phenomenon can be observed with the same genetic mutation in different background strains of mice, which allows for the identification of potential disease-modifying genes through unbiased mapping in hybrid mice. Using this approach, Dr. McNally identified a number of genes that modulate NMD, including latent transforming growth factor beta binding protein 4 (LTBP4, [9]) and annexin A6 [10]. Importantly, both of these findings led to the development of therapies that are currently being evaluated in preclinical models of NMD. Dr. McNally also discussed her work on the benefits of intermittent glucocorticoid administration (*versus* daily administration), which leads to epigenetic changes within skeletal muscle cells that promote a state of enhanced muscle repair without eliciting muscle atrophy [11]. Dr. McNally's Keynote Address offered an excellent example of how findings from fundamental research can be translated to potential therapies for the clinic.

SESSION 1: INNOVATIONS IN NEUROMUSCULAR DISEASE/ TRANSFORMATIVE TECHNOLOGIES

The first session was moderated by Drs. Jodi Warman-Chardon (TOH, CA) and Robin Parks (OHRI, CA). Professor Matthew Wood (University of Oxford, UK) highlighted the potential of oligonucleotide-based therapies, discussing some of the recent developments in oligonucleotide chemistry (*e.g.* controlled steriochemistry [12]) and delivery (*e.g.* peptide-conjugated oligonucleotides [13]). Such optimizations will undoubtedly enhance the safety and efficacy of this promising class of therapeutic. Professor Volker Staub (Newcastle University, UK) discussed the importance of world-wide collaborative ventures to coordinate and advance NMD clinical research. In addition to international efforts to simplify and standardize disease nomenclature [14], Professor Straub is involved in integrating clinical data from varied researchers, institutes and countries into a single database, including such efforts as MyoSHARE, Phenotips and several others [15–18].

Dr. Charlotte Sumner (Johns Hopkins University, US) discussed the exciting recent therapeutic developments for SMA, and overviewed challenges in achieving and determining clinical efficacy. For example, the antisense oligonucleotide medication nusinersen requires repeated intrathecal delivery. In addition, nusinersen efficacy appears to be related to location of intrathecal delivery (caudal better than rostal), variable uptake in different cell types, and potential epigenetic factors that might engage to counteract efficacy of the antisense oligonucleotide therapeutic [19]. Dr. Ronald Cohn (SickKids Children's Hospital, CA) presented his work on "interventional genomics". Dr. Cohn's research group has exploited the CRISPR/Cas9 system to develop therapies that can delete duplicated regions in the dystrophin gene [20], thus restoring gene function, or that use a cutting-inactive Cas9 fused to a transcriptional activator to upregulate laminin α2 expression for functional compensation in a mouse model of laminin α1 deficiency [21].

SESSION 2: NEW DEVELOPMENTS IN SPINAL MUSCULAR ATROPHY

Session 2 covered emerging disease discoveries in SMA and was moderated by Dr. Alex MacKenzie (CHEO, CA). Dr. Thomas Gillingwater (University of Edinburgh, UK) presented his efforts to analyse samples from patients with SMA to inform and refine new therapy development and optimization in the lab. Dr. Gillingwater presented his work on the timing and level of SMN protein expression in various tissues during development in patients [22], trying to answer the questions of when does SMA disease really start and what are the involvement and contributions of non-neuronal tissues in the disease [23]. Dr. Brunhilde Wirth (University of Cologne, DE) noted that SMA patients with the exact same mutation can present with varied disease severity, which is the foundation for her work to identify genetic modifiers of the disease. In addition to the major disease modifier, *SMN2*, Dr. Wirth discussed other genes that can significantly modify disease severity, including *PLS3* [24], *NCALD* [25] and *CHP1* [26], all of which may function through an ability to affect cellular

endocytosis. These genetic modifiers may serve as additional targets for therapeutic intervention to treat SMA either alone or in combination with SMN-directed therapies. Dr. Christian Lorson (University of Missouri, US) discussed his work on identifying new therapeutic targets in SMA, which potentially could be used in combination with existing therapeutics such as nusinersen. Based on an analysis of common transcriptome changes that occurred in susceptible and spared motor neurons in SMA, ALS and SMARD1-deficiency, the Lorson group identified α-synuclein as downregulated in all these disorders and, importantly, showed that vector-mediated expression of α-synuclein extended life in a mouse model of SMA [27]. Profiling of miRNA levels in derived motor neurons from induced pluripotent stem cell (iPSC) from SMA patient fibroblasts led to the identification of micro-RNA hsa-miR-23a-3p, which is also down regulated in a mouse model of SMA. Administration of an AAV vector expressing this miRNA resulted in widespread changes in gene expression, but not of *SMN* itself, and an extension in lifespan [28]. Finally, Dr. Melissa Bowerman (Keele University, UK) presented a short talk entitled, "Combining multi-omics and drug repositioning approaches to identify novel muscle-specific treatments for spinal muscular atrophy."

SESSION 3A: CLINICAL SESSION – ADVANCES IN CLINICAL MYOPATHIES

Dr. Pierre Bourque (TOH, CA) moderated this session dedicated to advances in diagnostics in clinical myopathies. Dr. Bernard Brais (McGill University, CA) began the session by presenting his work on Strongperson syndrome, which presents with muscle hypertrophy/superior strength, incapacitating myalgias, and muscle fatigability. By combining linkage analysis and exome sequencing of a large dominant French-Canadian family with the Strongperson phenotype, the Brais lab identified a segregating missense variant predicted to be damaging in the I-band protein *DCST2,* and causing dysregulation of skeletal muscle calcium homeostasis due to slow calcium reuptake. Dr. Nathalie Streichenberger (Université Claude Bernard Lyon, FR) provided a comprehensive overview of muscle biopsy techniques for genetic or acquired/inflammatory muscle diseases, including the importance of accurately documenting clinical information and ensuring that appropriate ethics approval are in place prior to obtaining the biopsy for clinical or research purposes [29]. Dr. Streichenberger highlighted the use and importance of clinical biopsy and immunohistochemistry techniques in a large international cohort of patients with Glycogen Storage Disorder type III (GSDIII), a rare metabolic disorder with liver, cardiac, and skeletal muscle involvement. Muscle biopsies in GSDIII patients revealed the presence of vacuoles filled with Periodic acid–Schiff-positive material, and electron microscopic data showed large non-membrane bound sarcoplasmic deposits of normally structured glycogen as well as smaller abnormal rounded sac structures containing glycogen and corresponding to autophagosomes [30]. Dr. Hanns Lochmüller (uOttawa, CA) described the classic diagnostic features of congenital myasthenic syndromes (CMS), including early onset of the disease and exercise-induced muscle weakness, as well as favourable response to medications such as acetylcholinesterase (AChE) inhibitors or beta-agonists [31, 32]. Dr. Lochmüller highlighted the diagnostic importance of next generation sequencing in the discovery of a new CMS caused by homozygous *SLC25A1* c.740G>A; p.(Arg247Gln) mutations, characterized by fatigability, weakness, ophthalmoparesis and mild cognitive impairment. Electron microscopy of muscle from two cases of *SLC25A1* mutations revealed enlarged and accumulated mitochondria [31–34]. A short talk was provided by Dr. Martine Tétreault (University of Montreal) entitled "Differential expression analysis to uncover fibre type disproportion".

SESSION 3B: BASIC RESEARCH SESSION – ADVANCES IN MUSCLE STEM CELLS AND DEVELOPMENT

The first basic research session was moderated by Dr. Nadine Wiper Bergeron (uOttawa, CA). Dr. Christophe Marcelle (University of Lyon, FR) described the advantages of chick embryos as a model system for human skeletal muscle development [35]. Using an siRNA-based screen, the Marcelle group was able to identify genes that could enhance or reduce myoblast fusion in chick embryos, including TGF-β family members which appear to be "molecular breaks" of cell fusion. These proteins appear to function through a receptor complementation mechanism to limit the degree of cell fusion and thus ensure natural muscle growth during regeneration. Inhibition of family member SMAD7 for example, led to greatly enhanced cell fusion that

could be exploited therapeutically to enhance muscle regeneration as an approach to combat disease. Dr. Emanuela Gussoni (Boston Children's Hospital, US) discussed her work on CD82, a tetraspanin protein found on satellite cells, and its potential role in disease [36]. Knockout of CD82 in mice did not lead to any noticeable defects in young mice [37]. However, there was some evidence of protein aggregation in muscle fibers from older mice. Mice defective in both dystrophin and CD82 showed a more severe disease, including muscle pathology, severe kyphosis and reduced muscle strength compared to either knockout alone. CD82 appears to exert its effects through multiple mechanisms at the level of both cell membrane and cellular vesicles. Dr. Thomas Rando (Stanford University, US) discussed his work on developing new approaches to more efficiently regenerate skeletal muscle fibers. His group developed two luciferase-based reporter mice that can be used to monitor global muscle degeneration and regeneration [38, 39], as well as the efficacy of therapeutics that impact these processes. For example, delivery of an AAV-microdystrophin to *mdx* mice also encoding the degenerative reporter protein allows for monitoring a relative decline in degeneration using non-invasive whole animal imaging [38]. Dr. Rando also presented his work on artificial muscle fibers that can be used to enhance the engraftment rate of transplanted myoblasts [40]. These fibers can be modified (*e.g.* coated with the basement membrane protein laminin), or co-seeded with other cell types naturally found in this tissue (*e.g.* immune cells, endothelial cells [41]) to provide a more accurate reflection of the natural stem cell niche [42]. The session ended with a short talk by Dr. Matthew Alexander (University of Alabama, US) entitled, "MicroRNA-486 regulates DMD pathology via targeting mRNAs that remodel the extracellular matrix".

SESSION 4A: CLINICAL SESSION: NEUROMUSCULAR CLINICAL CARE

This session devoted to recent advances in neuromuscular patient clinical care and management was moderated by Dr. Leanne Ward (CHEO, CA). Dr. Lawrence Korngut (The Hotchkiss Brain Institute, CA) described the Canadian Neuromuscular Disease Registry (CNDR), consisting of a network of 15 pediatric and 16 adult neuromuscular clinics from across Canada [43, 44]. Dr. Korngut outlined the SMA-specific dataset from 250 patients in the 31 Canadian neuromuscular clinics which can be used to provide real-world evidence to inform the current utilisation, effectiveness and safety of SMA treatments. The registries also provide valuable long-term data at a fraction of the cost of controlled studies [45]. CNDR registers patients with over 130 different NMD and serves to identify regional differences in patient care, for example discrepancies in ALS care among Canadian provinces at time of diagnosis, riluzole prescription and feeding tube use [46]. Dr. Gerald Pfeffer (The Hotchkiss Brain Institute, CA) described the combination of *SQSTM1* and *TIA1* variants as a novel genetic defect associated with myopathy; one proband carrying these two gene variants presented with myofibrillar myopathy, while two unrelated probands with the same genetic variants presented with a distal myopathy with rimmed vacuoles [47]. Dr. Pfeffer suggested that both genes should be investigated when considering a diagnosis for patients with rimmed vacuoles or myofibrillar myopathies. Dr. Bakri Elsheikh (Ohio State University, US) discussed SMA phenotypes based on *SMN2* copy number [48] and the typical pattern of early muscle weakness in adult patients with SMA (*e.g.* greater weakness of the triceps muscles compared to the biceps brachialis, greater weakness of the quadriceps relative to the biceps femoris). Dr. Elsheikh also reported that maximal voluntary isometric contraction testing and 6-minute walk test are suitable outcomes for use in ambulatory adults with SMA [49]. Dr. Pat Korathanakhun (McGill University) presented a short talk on "Folate deficiency polyneuropathy mimicking Guillain-Barre syndrome among Thai prisoners after the outbreak of H3N2 influenza: A case series study of clinical and electrophysiologic features."

SESSION 4B: BASIC RESEARCH SESSION – ADVANCES IN MUSCLE DISEASE PATHOGENESIS AND TREATMENT

Dr. Keir Menzies (uOttawa, CA) chaired the basic research session on muscle disease pathogenesis and treatment. Dr. Lawrence Hayward (Massachusetts General Hospital, US) provided an overview of the clinical presentation and genetics of facioscapulohumeral muscular dystrophy (FSHD), including the molecular features that are believed to cause the disease. Dr. Hayward then presented early results from his single cell analysis of gene expression in differentiated iPSC cells derived from FSHD patients,

which will complement similar work performed in human primary myoblasts [50]. Dr. Stephen Cannon (University of California Los Angeles, US) presented his research on answering the question of why patients with hypokalemic periodic paralysis, caused by mutations in voltage dependent sodium or calcium channels [51], suffer from attacks of paralysis only after the cessation of exercising. Dr. Cannon determined that the state of acidosis induced during exercise inhibits the paired chloride channels. During recovery from acidosis, chloride channels become activated, flooding the cell with chloride resulting in muscle paralysis [52]. Dr. Kevin Campbell (University of Iowa, US) discussed his work in characterizing the biogenesis of dystroglycan [53]. Dystroglycan protein is heavily glycosylated in a highly organized manner, with the majority of polysaccharide added by the LARGE protein. Mutations in dystroglycan, or any of the proteins responsible for glycosylating dystroglycan, give rise to Limb Girdle Muscular Dystrophy (LGMD). However, targeted upregulation of these same proteins to rescue the glycosylation status of dystroglycan could increase the interaction between the muscle cell and basement membrane, potentially acting to strengthen a dystrophic muscle fiber [54]. Dr. Katelyn Daman from the laboratory of Dr. Charles Emmerson Jr (University of Massachusetts Medical School, US) presented a short talk on her work entitled, "An innate immunity model of FSHD muscle pathology".

AN EVENING AT THE CANADIAN MUSEUM OF HISTORY

The Ottawa NMD 2019 conference gala was held at the Canadian Museum of History (Gatineau, Canada), with conference co-organizers Drs. Rashmi Kothary (OHRI, CA) and Bernard Jasmin (uOttawa, CA) acting as the Masters of Ceremony. Following the Gala Dinner, Ms. Sandra Plagakis provided a witty and inspirational talk as a person affected by NMD. Ms. Plagakis is a nationally recognized radio broadcast personality and frequently donates her time in support of many Canadian charities, including Muscular Dystrophy Canada, Children's Hospital of Eastern Ontario, Lanark County Interval House, and the Snowsuit Fund. Ms. Plagakis described her journey to diagnosis with myasthenia gravis, an odyssey filled with misdiagnosis and uncertainty that spanned many years. When finally appropriately diagnosed and started on an effective therapy, Ms. Plakagis had an astounding improvement in strength and quality of life. Ms. Plakagis' story reminded the audience of NMD basic and clinical researchers of the importance of early and accurate diagnosis, and of the extremely effective treatment responses that can be achieved in these disorders with appropriate therapy. The story served as inspiration to the audience and an additional reminder of the impact of our work on patients.

SESSION 5: CHALLENGES AND OPPORTUNITIES IN AMYOTROPHIC LATERAL SCLEROSIS

The session devoted to amyotrophic lateral sclerosis (ALS) was moderated by Dr. Ari Breiner (TOH, CA). Dr. Michael Benatar (University of Miami Health System, US) opened the session and described the importance of biomarkers in therapy development for ALS, including predictive, prognostic and pharmacodynamic markers. In general, current clinical outcome measures for ALS are insufficiently sensitive to see changes above natural variation, although several new potential biomarkers, such as neurofilament light chain, are showing some promise [55, 56]. Dr. Laura Ranum (University of Florida, US) discussed her work on repeat expansions in neurological disorders, focusing on C9orf72 in ALS. Transcription of these repeat expansions can give rise to repeat-associated non-ATG (RAN) translation, resulting in the production of various dipeptide proteins (depending on the reading frame) [57]. Interestingly, some long-term, non-progressing patients with repeat expansions in C9orf72 naturally have antibodies to these dipeptides, suggesting that such antibodies may function to sequester any toxic effects of these proteins. Indeed, antibodies generated against at least some dipeptide proteins can reduce disease symptoms in mice harboring a human allele of C9orf72 with a repeat expansion [57–59]. This finding holds great promise for treatment of ALS caused by repeat expansions within C9orf72, and possibly other repeat expansion disorders. Dr. Robert Baloh (Cedars Sinai, US) further highlighted C9orf72 and its role in neurodegeneration and neuroinflammation. Loss of even one copy of the C9orf72 gene in mice does not result in neurological deficits but is associated with immune defects [60]. Similarly, patients with ALS/FTD caused by C9orf72 show a higher incidence of autoimmune disease [61]. Dr. Baloh discussed his work on elucidating the specific cellular signaling pathways that are dysregulated in cells deficient in C9orf72 including the role

in altered immune function and neuroinflammation [62]. Dr. Sally Spendiff from the laboratory of Dr. Hanns Lochmüller (uOttawa, CA) provided a short talk entitled, "Modulation of the acetylcholine receptor clustering pathway improves neuromuscular junction structure and muscle strength in a mouse model of congenital myasthenic syndromes."

SESSION 6: PHENOTYPIC AND MOLECULAR INSIGHTS INTO MYOPATHIES

Session 6 was moderated by Dr. Jeffrey Dilworth (OHRI, CA). The presentation by Dr. Annemieke Aartsma-Rus (Leiden University, NL) is perhaps best summarized by one of her opening lines, "No model system is perfect, but that does not mean they are not useful." Dr. Aartsma-Rus discussed efforts in the research community to enhance scientific rigor and reproducibility of preclinical studies through the creation of standard operating procedures [63]. Dr. Michael Rudnicki (OHRI, CA) discussed his work on the role of primary cilia and sonic hedgehog (Shh) signaling is establishing the G_{Alert} state in muscle satellite cells. G_{Alert} satellite cells are quiescent but have an enhanced regenerative capacity [64]. Primary cilia act as "cellular antennae" that are essential for proper Shh signaling and are thus crucial for establishment of the G_{Alert} state. Dr. Carsten Bonnemann (National Institutes of Health, US) provided four stories regarding new phenotypes for old genes, including *TPM3* [65], *MYBPC1* [66], *TNNC2* and *UNC45B*. Although mutations in all four of these proteins lead to sarcomeric myopathies, the mechanism by which each causes disease is quite varied, leading to distinctly different phenotypes. Dr. Zakaria Orfi from the laboratory of Dr. Nicholas Dumont (CHU Sainte-Justine Research Center, CA) provided a short talk entitled, "Biallelic variants in the transcription factor PAX7 are a new genetic cause of myopathy".

SESSION 7A: CLINICAL SESSION – TRANSFORMATIVE TECHNOLOGIES IN THE CLINICAL WORLD

The clinical session on myopathies was moderated by Dr. Jocelyn Zwicker (TOH, CA). Dr. Jodi Warman-Chardon (TOH, CA) opened the session by discussing the use of emerging genomics technologies to diagnose patients with rare genetic NMD. Dr Warman-Chardon described the increasing use of next generation sequencing, including clinical RNA sequencing [67]. She highlighted the use of muscle magnetic resonance imaging (MRI) to help validate pathogenic genetic mutations [17, 67, 68] as well as identify more recently described inflammatory myopathy mimics that clinically resemble muscular dystrophies [69]. Dr. Jordi Diaz-Manera (Hospital Universitari de las Santa Creu i Sant Pau, Spain and Newcastle University, UK) outlined the importance of large international studies of patients with muscular dystrophies to help further refine muscle MRI as a diagnostic tool [68]. He described the use of muscle MRI to assess symmetry, gradient of fatty infiltration, and muscle texture in large international cohorts of patients with Pompe disease [70], dysferlinopathies [71] and sarcoglycanopathies [72]. Finally, Dr. Diaz-Manera described a novel muscle MRI-based artificial intelligence machine learning model that has very high diagnostic accuracy (>95%) compared to muscle MRI expert reviewers. Interestingly, pelvic muscles, which are not typically assessed clinically, were especially relevant for diagnosis with the machine learning model [73]. Dr. Stephan Züchner (University of Miami Health System, US) described the broad clinical continuum of axonopathies, with length-dependent degeneration of the long axons in the peripheral (Charcot-Marie-Tooth type 2 [CMT2]) and central (hereditary spastic paraplegia [HSP]) nervous systems [74]. Using the GENESIS genomic data-sharing platform to enable scientists and clinicians to share anonymized genomic information [75], Dr. Züchner identified *SIPA1L2* (signal-induced proliferation-associated 1 like 2A), part of a myelination-associated co-expressed network regulated by the master transcription factor SOX10, as a candidate modifier gene in CMT1A caused by *PMP22* mutations. Importantly, *in vitro* knockdown of SIPA1L2 in Schwannoma cells led to a significant reduction of PMP22 expression, suggesting a potential strategy for drug development in CMT1A [76]. Dr. David Pellerin (McGill University, CA) provided a short talk titled "Novel Recessive *TNNT1* Congenital Core-Rod Myopathy in French Canadians."

SESSION 7B: BASIC RESEARCH SESSION – MOTOR NEURONOPATHIES/MITOCHONDRIAL DISORDERS

The moderator for this session was Dr. Michael De Lisio (uOttawa, CA). Dr. Christine Vande Velde

(University of Montreal, CA) spoke on her work investigating the function of TDP-43 in ALS. Mutations in TDP-43 are directly causative of ALS, but the protein is also commonly mislocalized from the nucleus to the cytoplasm in motor neurons of patients with sporadic or familial ALS due to mutations in other disease-causing genes. TDP-43 is involved in stress granule formation, and Dr. Vande Velde discussed her work on TDP-43-mediated regulation of G3BP1, another protein necessary for stress granule formation [77]. Given the important role of G3BP1 in stress granule assembly [78], G3BP1 may be a genetic modifier of ALS. Dr. Carlos Moraes (University of Miami, US) noted that DNA in mitochondria is usually heteroplasmic (*i.e.* contains multiple copies of mitochondrial DNA of which some may carry a pathogenic mutation or be wildtype), which offers a unique opportunity for therapy. He showed that specific cleavage of the mitochondrial DNA containing the mutation, through targeting of specific nucleases using TALEN-meganuclease fusions or CRISPR/Cas9 technology, is followed by a restoration of DNA copy number primarily using the remaining mitochondrial chromosome containing the wildtype gene [79]. This approach was shown to work well in mice using an AAV9 to deliver the mitoTALEN [80]. Dr. Mary-Ellen Harper (uOttawa, CA) presented studies examining skeletal muscle OXPHOS dysfunction in chronic metabolic disease, and its role in obesity and type II diabetes. Dr. Harper's studies revealed that individuals who are resistant to the effects of dieting have a lower basal level of both muscle fatty acid oxidation and maximal oxidative phosphorylation relative to those who respond to dieting [81]. Diabetic obese individuals appear to have impaired mitochondrial supercomplex assembly, which may have implications in diabetic disease onset and pathogenesis [82]. Dr. Catheryn Lim from the laboratories of Professors Carlo Rinaldi and Matthew Wood (University of Oxford, UK) provided a short talk entitled, "AAV9-mediated delivery of androgen receptor isoform 2 ameliorates the disease phenotype in a mouse model of spinal and bulbar muscular atrophy".

SESSION 8: FUTURE DIRECTIONS IN NEUROMUSCULAR DISEASE RESEARCH

The final session of the conference was moderated by Drs. Jodi Warman-Chardon (TOH, CA) and Robin Parks (OHRI, CA). Dr. Rita Horvath (Cambridge University, UK) provided a talk entitled, "What causes tissue-specific phenotypes in mitochondrial disease?" For example, the nuclear-encoded glycyl-tRNA synthetase (GARS) gene is essential for protein translation in both the cytoplasm and mitochondria, but dominant mutations in GARS are associated with inherited neuropathies while recessive mutations cause severe childhood-onset disorders affecting skeletal and cardiac muscles [83]. In human-induced neuronal progenitor cells, both recessive and dominant mutations were associated with significant changes in mitochondrial respiratory chain complex subunits, Krebs cycle enzymes and transport proteins. However, proteins involved in fatty acid oxidation were only altered by recessive mutations, while changes in vesicle-associated membrane protein-associated protein B (VAPB), and its downstream pathways (*e.g.* mitochondrial calcium uptake and autophagy) were detected with dominant GARS mutations. Dr. Fabio Rossi (University of British Columbia, CA) discussed his work on unraveling the origin and role of macrophage in muscle regeneration [84]. Dr. Rossi showed that resident macrophages embedded within muscle are responsible for clearing damaged tissues and aiding muscle regeneration, a function that cannot be accomplished by circulating macrophages. Thus, these non-canonical functions of macrophages are crucial in development, regeneration and tissue repair. Dr. Charles Thornton (University of Rochester Medical Centre, US) discussed the potential underlying molecular etiology for myotonic dystrophy type 1 (DM1), and the quest for biomarkers for the disease. The CUG repeat expansion present in mRNA from the mutant *DMPK* gene results in sequestration of MBNL1 [85], a protein implicated in alternative splicing. Thus, reduced abundance of MBNL1 causes aberrant splicing of certain mRNAs, which can be detected in biopsies from patients, raising the possibility of a specific biomarker signature of the disease and response to potential therapeutics [86]. Unfortunately, patients showed significant natural variation in the degree of mis-splicing, reducing the accuracy of this signature as an outcome measure. Thus, the quest for effective biomarkers for DM1 continues.

CONCLUDING REMARKS

On behalf of the organizing committee, final remarks were provided by Drs. Jodi Warman-Chardon (TOH, CA) and Robin Parks (OHRI, CA),

who thanked the attendees, speakers and sponsors. The goal was to provide an international forum for exchange of data, information and ideas to strengthen existing collaborations and develop new ones while also promoting innovation that is essential to increase our understanding of NMD disease pathogenesis, ultimately enhancing diagnosis and treatment options for patients affected by NMD. Unfortunately, due to the COVID-19 pandemic, the Ottawa NMD 2021 conference scheduled for October 2021 was cancelled. However, plans are now well underway for the Ottawa NMD 2023 conference, tentatively scheduled for September 7-9, 2023.

ACKNOWLEDGMENTS

As with the prior four conferences, the conference organizers are extremely indebted to Ms. Heidi Hickey (OHRI) for her attention to detail and tireless efforts to ensure that the conference was efficiently organized. We also thank Michael Hendley (OHRI) and his team for preparing and managing our online website and registration system. Finally, we sincerely thank all our speakers, moderators and attendees for their enthusiastic participation in Ottawa.

The Conference was kindly supported by unrestricted educational funds provided by the following: Platinum Sponsors – Ottawa Hospital Research Institute, University of Ottawa (Faculty of Medicine, Brain and Mind Research Institute), Muscular Dystrophy Canada, Canadian Institutes of Health Research (Institutes of Genetics and Musculoskeletal Health and Arthritis), PTC Therapeutics, Sarepta Therapeutics, Akcea Therapeutics Canada, Roche, Alexion.

Gold Sponsors – Alnylam Pharmaceuticals, Biogen, Mitsubishi Tanabe Pharma Canada, Grifols.

Silver Sponsor – CSL Behring, Children's Hospital of Eastern Ontario Research Institute, Aurora Scientific.

Authors declared no conflict of interests.

REFERENCES

[1] Deenen JC, Horlings CG, Verschuuren JJ, Verbeek AL, van Engelen BG. The Epidemiology of Neuromuscular Disorders: A Comprehensive Overview of the Literature. J Neuromuscul Dis. 2015;2(1):73-85.

[2] Emery AE. Population frequencies of inherited neuromuscular diseases–a world survey. Neuromuscul Disord. 1991;1(1):19-29.

[3] Norwood FL, Harling C, Chinnery PF, Eagle M, Bushby K, Straub V. Prevalence of genetic muscle disease in Northern England: In-depth analysis of a muscle clinic population. Brain. 2009;132(Pt 11):3175-86.

[4] Chelban V, Wilson MP, Warman Chardon J, Vandrovcova J, Zanetti MN, Zamba-Papanicolaou E, et al. PDXK mutations cause polyneuropathy responsive to pyridoxal 5'-phosphate supplementation. Ann Neurol. 2019;86(2):225-40.

[5] Roy B, Griggs R. Advances in Treatments in Muscular Dystrophies and Motor Neuron Disorders. Neurol Clin. 2021;39(1):87-112.

[6] Chardon JW, Jasmin BJ, Kothary R, Parks RJ. Report on the 3rd Ottawa International Conference on Neuromuscular Biology, Disease and Therapy - September 24-26, 2015, Ottawa, Canada. J Neuromuscul Dis. 2016;3(3): 431-42.

[7] Chardon JW, Jasmin BJ, Kothary R, Parks RJ. Report on the 4th Ottawa International Conference on Neuromuscular Disease and Biology - September 5-7, 2017, Ottawa, Canada. J Neuromuscul Dis. 2018;5(4):539-52.

[8] Ferrier A, Ryan SD, Kothary R, McNally EM. New Directions in Biology and Disease of Skeletal Muscle, Meeting Report, 5–8 May 2010, Ottawa, Canada. Neuromuscular Disorders. 2011;21(2):157-9.

[9] Heydemann A, Ceco E, Lim JE, Hadhazy M, Ryder P, Moran JL, et al. Latent TGF-beta-binding protein 4 modifies muscular dystrophy in mice. J Clin Invest. 2009;119(12):3703-12.

[10] Swaggart KA, Demonbreun AR, Vo AH, Swanson KE, Kim EY, Fahrenbach JP, et al. Annexin A6 modifies muscular dystrophy by mediating sarcolemmal repair. Proc Natl Acad Sci U S A. 2014;111(16):6004-9.

[11] Quattrocelli M, Barefield DY, Warner JL, Vo AH, Hadhazy M, Earley JU, et al. Intermittent glucocorticoid steroid dosing enhances muscle repair without eliciting muscle atrophy. J Clin Invest. 2017;127(6):2418-32.

[12] Iwamoto N, Butler DCD, Svrzikapa N, Mohapatra S, Zlatev I, Sah DWY, et al. Control of phosphorothioate stereochemistry substantially increases the efficacy of antisense oligonucleotides. Nat Biotechnol. 2017;35(9):845-51.

[13] Klein AF, Varela MA, Arandel L, Holland A, Naouar N, Arzumanov A, et al. Peptide-conjugated oligonucleotides evoke long-lasting myotonic dystrophy correction in patient-derived cells and mice. J Clin Invest. 2019;129(11):4739-44.

[14] Straub V, Murphy A, Udd B. 229th ENMC international workshop: Limb girdle muscular dystrophies - Nomenclature and reformed classification Naarden, the Netherlands, 17-19 March 2017. Neuromuscul Disord. 2018;28(8):702-10.

[15] Girdea M, Dumitriu S, Fiume M, Bowdin S, Boycott KM, Chenier S, et al. PhenoTips: Patient phenotyping software for clinical and research use. Hum Mutat. 2013;34(8):1057-65.

[16] Johnson K, Bertoli M, Phillips L, Topf A, Van den Bergh P, Vissing J, et al. Detection of variants in dystroglycanopathy-associated genes through the application of targeted whole-exome sequencing analysis to a large cohort of patients with unexplained limb-girdle muscle weakness. Skelet Muscle. 2018;8(1):23.

[17] Warman Chardon J, Diaz-Manera J, Tasca G, Bonnemann CG, Gomez-Andres D, Heerschap A, et al. MYO-MRI diagnostic protocols in genetic myopathies. Neuromuscul Disord. 2019;29(11):827-41.

[18] Warman Chardon J, Straub V. The Role of Muscle Imaging in the Diagnosis and Assessment of Children with Genetic Muscle Disease. Neuropediatrics. 2017;48(4):233-41.

[19] Ramos DM, d'Ydewalle C, Gabbeta V, Dakka A, Klein SK, Norris DA, et al. Age-dependent SMN expression in disease-relevant tissue and implications for SMA treatment. J Clin Invest. 2019;129(11):4817-31.
[20] Wong TWY, Cohn RD. Therapeutic Applications of CRISPR/Cas for Duchenne Muscular Dystrophy. Curr Gene Ther. 2017;17(4):301-8.
[21] Kemaladewi DU, Bassi PS, Erwood S, Al-Basha D, Gawlik KI, Lindsay K, et al. A mutation-independent approach for muscular dystrophy via upregulation of a modifier gene. Nature. 2019;572(7767):125-30.
[22] Groen EJN, Perenthaler E, Courtney NL, Jordan CY, Shorrock HK, van der Hoorn D, et al. Temporal and tissue-specific variability of SMN protein levels in mouse models of spinal muscular atrophy. Hum Mol Genet. 2018;27(16):2851-62.
[23] Hamilton G, Gillingwater TH. Spinal muscular atrophy: Going beyond the motor neuron. Trends Mol Med. 2013;19(1):40-50.
[24] Hosseinibarkooie S, Peters M, Torres-Benito L, Rastetter RH, Hupperich K, Hoffmann A, et al. The Power of Human Protective Modifiers: PLS3 and CORO1C Unravel Impaired Endocytosis in Spinal Muscular Atrophy and Rescue SMA Phenotype. Am J Hum Genet. 2016;99(3):647-65.
[25] Riessland M, Kaczmarek A, Schneider S, Swoboda KJ, Lohr H, Bradler C, et al. Neurocalcin Delta Suppression Protects against Spinal Muscular Atrophy in Humans and across Species by Restoring Impaired Endocytosis. Am J Hum Genet. 2017;100(2):297-315.
[26] Janzen E, Mendoza-Ferreira N, Hosseinibarkooie S, Schneider S, Hupperich K, Tschanz T, et al. CHP1 reduction ameliorates spinal muscular atrophy pathology by restoring calcineurin activity and endocytosis. Brain. 2018;141(8):2343-61.
[27] Kline RA, Kaifer KA, Osman EY, Carella F, Tiberi A, Ross J, et al. Comparison of independent screens on differentially vulnerable motor neurons reveals alpha-synuclein as a common modifier in motor neuron diseases. PLoS Genet. 2017;13(3):e1006680.
[28] Kaifer KA, Villalon E, O'Brien BS, Sison SL, Smith CE, Simon ME, et al. AAV9-Mediated Delivery of miR-23a Reduces Disease Severity in Smn2B-/SMA Model Mice. Hum Mol Genet. 2019;28(19):3199-3210.
[29] Gallay L, Hot A, Petiot P, Thivolet-Bejui F, Maucort-Boulch D, Streichenberger N. Focal myositis: New insights on diagnosis and pathology. Neurology. 2018;90(12): e1013-e20.
[30] Laforet P, Inoue M, Goillot E, Lefeuvre C, Cagin U, Streichenberger N, et al. Deep morphological analysis of muscle biopsies from type III glycogenesis (GSDIII), debranching enzyme deficiency, revealed stereotyped vacuolar myopathy and autophagy impairment. Acta Neuropathol Commun. 2019;7(1):167.
[31] Thompson R, Abicht A, Beeson D, Engel AG, Eymard B, Maxime E, et al. A nomenclature and classification for the congenital myasthenic syndromes: Preparing for FAIR data in the genomic era. Orphanet J Rare Dis. 2018;13(1):211.
[32] Thompson R, Bonne G, Missier P, Lochmuller H. Targeted therapies for congenital myasthenic syndromes: Systematic review and steps towards a treatabolome. Emerg Top Life Sci. 2019;3(1):19-37.
[33] Balaraju S, Topf A, McMacken G, Kumar VP, Pechmann A, Roper H, et al. Congenital myasthenic syndrome with mild intellectual disability caused by a recurrent SLC25A1 variant. Eur J Hum Genet. 2020;28(3):373-7.
[34] Chaouch A, Porcelli V, Cox D, Edvardson S, Scarcia P, De Grassi A, et al. Mutations in the Mitochondrial Citrate Carrier SLC25A1 are Associated with Impaired Neuromuscular Transmission. J Neuromuscul Dis. 2014;1(1):75-90.
[35] Hirst CE, Marcelle C. The avian embryo as a model system for skeletal myogenesis. Results Probl Cell Differ. 2015;56:99-122.
[36] Alexander MS, Rozkalne A, Colletta A, Spinazzola JM, Johnson S, Rahimov F, et al. CD82 Is a Marker for Prospective Isolation of Human Muscle Satellite Cells and Is Linked to Muscular Dystrophies. Cell Stem Cell. 2016;19(6):800-7.
[37] Hall A, Fontelonga T, Wright A, Bugda Gwilt K, Widrick J, Pasut A, et al. Tetraspanin CD82 is necessary for muscle stem cell activation and supports dystrophic muscle function. Skelet Muscle. 2020;10(1):34.
[38] Filareto A, Maguire-Nguyen K, Gan Q, Aldanondo G, Machado L, Chamberlain JS, et al. Monitoring disease activity noninvasively in the mdx model of Duchenne muscular dystrophy. Proc Natl Acad Sci U S A. 2018;115(30):7741-6.
[39] Maguire KK, Lim L, Speedy S, Rando TA. Assessment of disease activity in muscular dystrophies by noninvasive imaging. J Clin Invest. 2013;123(5):2298-305.
[40] Quarta M, Brett JO, DiMarco R, De Morree A, Boutet SC, Chacon R, et al. An artificial niche preserves the quiescence of muscle stem cells and enhances their therapeutic efficacy. Nat Biotechnol. 2016;34(7):752-9.
[41] Tabula-Muris-Consortium. Single-cell transcriptomics of 20 mouse organs creates a Tabula Muris. Nature. 2018;562(7727):367-72.
[42] Rando TA, Ambrosio F. Regenerative Rehabilitation: Applied Biophysics Meets Stem Cell Therapeutics. Cell Stem Cell. 2018;22(3):306-9.
[43] Hodgkinson V, Lounsberry J, M'Dahoma S, Russell A, Benstead T, Brais B, et al. The Canadian Neuromuscular Disease Registry 2010-2019: A Decade of Facilitating Clinical Research Through a Nationwide, Pan-Neuromuscular Disease Registry. J Neuromuscul Dis. 2021;8(1):53-61.
[44] Korngut L, Campbell C, Johnston M, Benstead T, Genge A, Mackenzie A, et al. The CNDR: Collaborating to translate new therapies for Canadians. Can J Neurol Sci. 2013;40(5):698-704.
[45] Hodgkinson VL, Oskoui M, Lounsberry J, M'Dahoma S, Butler E, Campbell C, et al. A National Spinal Muscular Atrophy Registry for Real-World Evidence. Can J Neurol Sci. 2020;47(6):810-5.
[46] Hodgkinson VL, Lounsberry J, Mirian A, Genge A, Benstead T, Briemberg H, et al. Provincial Differences in the Diagnosis and Care of Amyotrophic Lateral Sclerosis. Can J Neurol Sci. 2018;45(6):652-9.
[47] Niu Z, Pontifex CS, Berini S, Hamilton LE, Naddaf E, Wieben E, et al. Myopathy With SQSTM1 and TIA1 Variants: Clinical and Pathological Features. Front Neurol. 2018;9:147.
[48] Elsheikh B, Prior T, Zhang X, Miller R, Kolb SJ, Moore D, et al. An analysis of disease severity based on SMN2 copy number in adults with spinal muscular atrophy. Muscle Nerve. 2009;40(4):652-6.
[49] Waldrop MA, Elsheikh BH. Spinal Muscular Atrophy in the Treatment Era. Neurol Clin. 2020;38(3):505-18.
[50] van den Heuvel A, Mahfouz A, Kloet SL, Balog J, van Engelen BGM, Tawil R, et al. Single-cell RNA sequencing in facioscapulohumeral muscular dystrophy disease etiology and development. Hum Mol Genet. 2019;28(7):1064-75.
[51] Cannon SC. Channelopathies of skeletal muscle excitability. Compr Physiol. 2015;5(2):761-90.

[52] Mi W, Wu F, Quinonez M, DiFranco M, Cannon SC. Recovery from acidosis is a robust trigger for loss of force in murine hypokalemic periodic paralysis. J Gen Physiol. 2019;151(4):555-66.
[53] Yoshida-Moriguchi T, Campbell KP. Matriglycan: A novel polysaccharide that links dystroglycan to the basement membrane. Glycobiology. 2015;25(7):702-13.
[54] Goddeeris MM, Wu B, Venzke D, Yoshida-Moriguchi T, Saito F, Matsumura K, et al. LARGE glycans on dystroglycan function as a tunable matrix scaffold to prevent dystrophy. Nature. 2013;503(7474):136-40.
[55] Benatar M, Boylan K, Jeromin A, Rutkove SB, Berry J, Atassi N, et al. ALS biomarkers for therapy development: State of the field and future directions. Muscle Nerve. 2016;53(2):169-82.
[56] Benatar M, Turner MR, Wuu J. Defining pre-symptomatic amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(5-6):303-9.
[57] Zu T, Gibbens B, Doty NS, Gomes-Pereira M, Huguet A, Stone MD, et al. Non-ATG-initiated translation directed by microsatellite expansions. Proc Natl Acad Sci U S A. 2011;108(1):260-5.
[58] Nguyen L, Cleary JD, Ranum LPW. Repeat-Associated Non-ATG Translation: Molecular Mechanisms and Contribution to Neurological Disease. Annu Rev Neurosci. 2019;42:227-47.
[59] Nguyen L, Montrasio F, Pattamatta A, Tusi SK, Bardhi O, Meyer KD, et al. Antibody Therapy Targeting RAN Proteins Rescues C9 ALS/FTD Phenotypes in C9orf72 Mouse Model. Neuron. 2020;105(4):645-662.e11.
[60] O'Rourke JG, Bogdanik L, Yanez A, Lall D, Wolf AJ, Muhammad AK, et al. C9orf72 is required for proper macrophage and microglial function in mice. Science. 2016;351(6279):1324-9.
[61] Miller ZA, Sturm VE, Camsari GB, Karydas A, Yokoyama JS, Grinberg LT, et al. Increased prevalence of autoimmune disease within C9 and FTD/MND cohorts: Completing the picture. Neurol Neuroimmunol Neuroinflamm. 2016;3(6):e301.
[62] McCauley ME, Baloh RH. Inflammation in ALS/FTD pathogenesis. Acta Neuropathol. 2019;137(5):715-30.
[63] Willmann R, Buccella F, De Luca A, Grounds MD. 227(th) ENMC International Workshop:: Finalizing a plan to guarantee quality in translational research for neuromuscular diseases Heemskerk, Netherlands, 10-11 February 2017. Neuromuscul Disord. 2018;28(2):185-92.
[64] Rodgers JT, King KY, Brett JO, Cromie MJ, Charville GW, Maguire KK, et al. mTORC1 controls the adaptive transition of quiescent stem cells from G0 to G(Alert). Nature. 2014;510(7505):393-6.
[65] Donkervoort S, Papadaki M, de Winter JM, Neu MB, Kirschner J, Bolduc V, et al. TPM3 deletions cause a hypercontractile congenital muscle stiffness phenotype. Ann Neurol. 2015;78(6):982-94.
[66] Stavusis J, Lace B, Schafer J, Geist J, Inashkina I, Kidere D, et al. Novel mutations in MYBPC1 are associated with myogenic tremor and mild myopathy. Ann Neurol. 2019;86(1):129-42.
[67] Chardon JW, Smith AC, Woulfe J, Pena E, Rakhra K, Dennie C, et al. LIMS2 mutations are associated with a novel muscular dystrophy, severe cardiomyopathy and triangular tongues. Clin Genet. 2015;88(6):558-64.
[68] Warman Chardon J, Diaz-Manera J, Tasca G, Straub V. 247th ENMC International Workshop: Muscle magnetic resonance imaging - Implementing muscle MRI as a diagnostic tool for rare genetic myopathy cohorts. Hoofddorp, The Netherlands, September 2019. Neuromuscul Disord. 2020;30(11):938-47.
[69] Mohassel P, Landon-Cardinal O, Foley AR, Donkervoort S, Pak KS, Wahl C, et al. Anti-HMGCR myopathy may resemble limb-girdle muscular dystrophy. Neurol Neuroimmunol Neuroinflamm. 2019;6(1):e523.
[70] Nunez-Peralta C, Alonso-Perez J, Llauger J, Segovia S, Montesinos P, Belmonte I, et al. Follow-up of late-onset Pompe disease patients with muscle magnetic resonance imaging reveals increase in fat replacement in skeletal muscles. J Cachexia Sarcopenia Muscle. 2020;11(4):1032-46.
[71] Diaz-Manera J, Fernandez-Torron R, J LL, James MK, Mayhew A, Smith FE, et al. Muscle MRI in patients with dysferlinopathy: Pattern recognition and implications for clinical trials. J Neurol Neurosurg Psychiatry. 2018;89(10):1071-81.
[72] Alonso-Perez J, Gonzalez-Quereda L, Bello L, Guglieri M, Straub V, Gallano P, et al. New genotype-phenotype correlations in a large European cohort of patients with sarcoglycanopathy. Brain. 2020;143(9):2696-708.
[73] Verdu-Diaz J, Alonso-Perez J, Nunez-Peralta C, Tasca G, Vissing J, Straub V, et al. Accuracy of a machine learning muscle MRI-based tool for the diagnosis of muscular dystrophies. Neurology. 2020;94(10):e1094-e102.
[74] Bis-Brewer DM, Gan-Or Z, Sleiman P, Hakonarson H, Fazal S, Courel S, et al. Assessing non-Mendelian inheritance in inherited axonopathies. Genet Med. 2020;22(12):2114-9.
[75] Gonzalez M, Falk MJ, Gai X, Postrel R, Schule R, Zuchner S. Innovative genomic collaboration using the GENESIS (GEM.app) platform. Hum Mutat. 2015;36(10):950-6.
[76] Tao F, Beecham GW, Rebelo AP, Svaren J, Blanton SH, Moran JJ, et al. Variation in SIPA1L2 is correlated with phenotype modification in Charcot- Marie- Tooth disease type 1A. Ann Neurol. 2019;85(3):316-30.
[77] McDonald KK, Aulas A, Destroismaisons L, Pickles S, Beleac E, Camu W, et al. TAR DNA-binding protein 43 (TDP-43) regulates stress granule dynamics via differential regulation of G3BP and TIA-1. Hum Mol Genet. 2011;20(7):1400-10.
[78] Aulas A, Caron G, Gkogkas CG, Mohamed NV, Destroismaisons L, Sonenberg N, et al. G3BP1 promotes stress-induced RNA granule interactions to preserve polyadenylated mRNA. J Cell Biol. 2015;209(1):73-84.
[79] Pereira CV, Bacman SR, Arguello T, Zekonyte U, Williams SL, Edgell DR, et al. mitoTev-TALE: A monomeric DNA editing enzyme to reduce mutant mitochondrial DNA levels. EMBO Mol Med. 2018;10(9):e8084.
[80] Bacman SR, Kauppila JHK, Pereira CV, Nissanka N, Miranda M, Pinto M, et al. MitoTALEN reduces mutant mtDNA load and restores tRNA(Ala) levels in a mouse model of heteroplasmic mtDNA mutation. Nat Med. 2018;24(11):1696-700.
[81] Thrush AB, Antoun G, Nikpay M, Patten DA, DeVlugt C, Mauger JF, et al. Diet-resistant obesity is characterized by a distinct plasma proteomic signature and impaired muscle fiber metabolism. Int J Obes (Lond). 2018;42(3):353-62.
[82] Antoun G, McMurray F, Thrush AB, Patten DA, Peixoto AC, Slack RS, et al. Impaired mitochondrial oxidative phosphorylation and supercomplex assembly in rectus abdominis muscle of diabetic obese individuals. Diabetologia. 2015;58(12):2861-6.
[83] Boczonadi V, Meyer K, Gonczarowska-Jorge H, Griffin H, Roos A, Bartsakoulia M, et al. Mutations in glycyl-tRNA

synthetase impair mitochondrial metabolism in neurons. Hum Mol Genet. 2018;27(12):2187-204.

[84] Theret M, Mounier R, Rossi F. The origins and non-canonical functions of macrophages in development and regeneration. Development. 2019;146(9):dev156000.

[85] Miller JW, Urbinati CR, Teng-Umnuay P, Stenberg MG, Byrne BJ, Thornton CA, et al. Recruitment of human muscleblind proteins to (CUG)(n) expansions associated with myotonic dystrophy. Embo J. 2000;19(17):4439-48.

[86] Wang ET, Treacy D, Eichinger K, Struck A, Estabrook J, Olafson H, et al. Transcriptome alterations in myotonic dystrophy skeletal muscle and heart. Hum Mol Genet. 2019;28(8):1312-21.