supported robust cellular growth, while the p.A397T-*MARS* insert did not support cellular growth confirming deleterious effect of this variant. **Conclusions:** Our patient's phenotype was similar to children with motor-predominant *GARS* mutations. Functional data notes this *MARS* variant to be damaging and predictive of a severe, early-onset phenotype.

P.071

Novel mutations in SPG7 identified from patients with late-onset spasticity

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Background: Hereditary spastic paraplegia (HSP) is a group of genetic diseases that cause progressive degeneration of the corticospinal tract. Historically, this disease was divided into two types:the classic subtype, with leg weakness and hypertonic bladder, and the complicated subtype, with features such as cerebellar ataxia or optic atrophy.Mutations in *SPG7 (*encoding paraplegin) leads to complicated HSP causing cerebellar ataxia, progressive external ophthalmoplegia in addition to the classical symptoms. AFG3L2 is a binding partner of paraplegin and mutations in *AFG3L2* cause a similar syndrome **Methods:** From a neurogenetic clinic , we identified 11 patients with late-onset HSP. Sequencing of *SPG7* and *AFG3L2* was performed using a customised assay, and/or clinical diagnostic sequencing panels.*SPG7* transcript level quantification was performed from whole blood RNA on a digital droplet qPCR system. **Results:** We identified 4 patients with pathogenic variants or variants of unknown significance in *SPG7*. No *AFG3L2* mutations were identified. We provide evidence for pathogenicity for three mutations that were not previously associated with SPG7-related disease, based on their occurrence in context of the correct phenotype, and the reduction of transcript levels measured with RT-qPCR.A curious association of the heterozygous p.Gly349Ser mutation in association with an ALS-like syndrome is reported. **Conclusions:** *SPG7* mutations sequencing has high diagnostic yield in late onset paraparesis

P.072

Agreement between children and their parents' ratings of the health-related quality of life of children with Duchenne Muscular Dystrophy

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Background: When measuring young Duchenne Muscular Dystrophy (DMD) patients' health-related quality of life (HRQoL), parent-proxy reports are heavily relied on. Therefore, it is imperative that the relationship between parent-proxy and child self-report HRQoL is understood. This study examined the level of agreement between children and their parent-proxy rating of the child's HRQoL. **Methods:** We used FOR-DMD clinical trial baseline data. HRQoL, measured using the PedsQL inventory, was reported by 178 parent and child (ages 4 to 7 years) dyads. Intracorrelation coefficients (ICC) measured absolute agreement while paired t-tests determined differences in the average HRQoL ratings between groups. **Results:** The level of agreement between child and parent-proxy ratings of HRQoL was poor for the generic PedsQL scale (ICC: 0.29) and its subscales; and, similarly low for the neuromuscular disease module (ICC:0.16). On average, parents rated their child's HRQoL as poorer than the children rated themselves in all scales except for psychosocial and school functioning. **Conclusions:** Child and parent-proxy HRQoL ratings are discordant in this study sample, as occurs in other chronic pediatric diseases. This should be taken into account when interpreting clinical and research HRQoL findings in this population. Future studies should examine reasons for parents' perception of poorer HRQoL than that reported by their children.

P.073

Cardiac dysfunction in mitochondrial disease: systematic review and metaanalysis

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Background: Cardiac dysfunction has significant impact on morbidity and mortality in patients with mitochondrial disorders. Cardiac screening tests are generally recommended because cardiac dysfunction can occur at any point in the disease course, and is amenable to treatment. However there is no clear evidence indicating the best screening strategy in patients with mitochondrial myopathy. **Methods:** Systematic review of the literature for cardiac investigations in adult patients with mitochondrial myopathy. We considered 1303 relevant abstracts, from which 58 full-length articles were reviewed. Seventeen articles including 701 total participants met inclusion criteria. Data extracted included age, diagnosis, and results from ECG, echocardiogram, cardiac MRI, nuclear medicine studies, and Holter monitor. **Results:** We identified echocardiogram and ECG as the principal screening modalities, that identify cardiac structural (26%) and conduction abnormalities (37%) in patients from various mitochondrial myopathy syndromes. Holter monitor was not a high yield investigation and limited studies were identified using cardiac MRI or nuclear medicine. **Conclusions:** We recommend screening with ECG and echocardiogram every 1-2 years in MERRF/MELAS, and every 3-5 years in milder syndromes when cardiac symptoms are not present. Only five of the included studies provided any follow-up data. We recommend studies of natural history, therapeutic response, and of cardiac MRI as areas for future study.

P.074

Clinical features of a family with distal myopathy and rimmed vacuoles due to a digenic interaction

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Background: The interaction between mutations in two or more genes is increasingly recognised as an important contributor to the phenotypic variability in genetic disorders. Co-occurrence of variants in SQSTM1 and TIA1 is reported as a cause of myopathy

in 3 prior cases, but limited clinical data were presented. We present detailed clinical features of a family with two siblings having a distal myopathy with rimmed vacuoles (DMRV), and genetic variants in SQSTM1 and TIA1. **Methods:** Clinicopathologic study of a family with DMRV to describe clinical features, laboratory and neurophysiology studies, neuroimaging, and genetic sequencing. **Results:** Two siblings with variants in SQSTM1 and TIA1 developed myopathy in their early 60's, with early involvement of ankle dorsiflexors and finger extensors. A decade after onset, patients remain ambulatory and have not developed cardiac or respiratory complications. MRI of the legs showed selective involvement of adductor magnus, vastus lateralis, and in lower legs the anterior compartment and medial gastrocnemius. Muscle pathology demonstrated rimmed vacuoles, disrupted myofibrillar architecture, and mislocalised TDP43. Two unaffected family members had one genetic variant but not both. **Conclusions:** We describe a fourth family with co-occurrence of TIA1 and SQSTM1 genetic variants and describe their detailed phenotype. Future study should address the mechanism of the interaction between these two variants.

P.075

Inflammatory Myositis associated with Myasthenia Gravis with and without thymic pathology: case series and literature review

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Background: The association of myasthenia gravis (MG) and inflammatory myositis (IM) is rare and often only one of the diseases is diagnosed. **Methods:** In this study, we reviewed medical records of patients seen at NMDU from 2004 to 2017 who had diagnosis of concurrent MG and IM. The data is presented descriptively. **Results:** We identified 7 patients with MG-IM overlap. Clinical features, laboratory and pathology data of the patients are summarized in Table 1. **Conclusions:** This is one of the largest case series with MG-IM overlap. It is very important to recognize such association and the different pattern of muscle involvement because therapies may be adjusted to treat both conditions. In patients with thymic pathology, conventional disease modifying agents, IVIG and glucocorticoid in addition to thymoma resection appear to be effective. In patients with refractory MG and myositis who were AChR negative, rituximab may be effective.

P.076

Safety of Eteplirsen, a phosphorodiamidate morpholino oligomer, in Duchenne Muscular Dystrophy patients amenable to Exon 51 skipping

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Background: Duchenne muscular dystrophy (DMD) is an X-linked disorder affecting 1:3500-5000 live male births, causing a life-limiting form of muscular dystrophy. Whole exon deletions disrupting the reading frame result in near-absence of sarcolemmal dystrophin, essential for muscle function. Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to induce production of internally-truncated dystrophin in certain patients. **Methods:** As of June 2016, 150 patients (4-19 years of age) with DMD received eteplirsen in 7 clinical trials. 143 patients received ≥1 intravenous infusion of eteplirsen (range: 0.5 - 50 mg/kg). 81 (54%) received treatment for ≥1 year (Range: 1-4+ years). **Results:** Common (≥15%) adverse events (AEs) were cough, headache, vomiting, back pain, extremity pain, contusion, nasopharyngitis, upper respiratory tract infection, nasal congestion, arthralgia and rash. Non-serious facial flushing, erythema and mild transient temperature elevation occurred with eteplirsen. 10 (6.7%) patients experienced severe AEs; 12 (8%) patients experienced serious AEs. All serious and all but 1 severe AEs were considered unrelated to eteplirsen by the treating physicians. Serial echocardiograms in 12 treated patients demonstrated no functional decline over 4+ years. **Conclusions:** Eteplirsen's tolerability will continue to be assessed in ongoing clinical trials.

An updated data summary will be presented.

P.077

Utility of a next generation sequencing in the diagnosis of Congenital Myasthenic Syndromes

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Background: Congenital Myasthenic Syndromes (CMS) are heterogeneous disorders caused by genetically determined structural or functional differences in proteins involved with the neuromuscular junctions. Clinical and molecular genetics studies of CMS patients have revealed significant locus heterogeneity; there are 21 known genes related to CMS, but other genes may mimic the phenotype, justifying the use of a multi-gene panel for genetic testing **Methods:** Our group developed custom sequence capture probes designed to flank 27 different genes associated with CMS, including enrichment for all coding exons as well the flanking intronic regions. We enrolled 20 patients from the paediatric and adult neuromuscular clinic with a clinical phenotype of CMS. Using custom analytical, we assessed the sequence variants and exon-level CNVs for each patient. **Results:** Thirteen male and seven female patients with median age of 12.25 years (range 1.5-39y) were assessed. We identified missense and CNVs in 17 patients, including established pathogenic mutations confirming the diagnosis in 5 patients **Conclusions:** The use of Next Generation Sequence with CNV for CMS can help determine the underlying causes of most CMS disorders and allow appropriate medical treatment, refined genetic counseling, and improved understanding of prognosis, justifying the implementation in the standard clinical screening of CMS.