fiber size variability, fibrosis, and pronounced fat infiltration, but no fiber type grouping, uniformity or fiber type size disproportion. Her disease was slowly progressing. At the current age of 8 years, she is unable to squat or lift her hands above her head and she needs help in daily activities. She has generalised muscular atrophy, and EMG shows progressive ubiquitous myogenic involvement. Sequencing of a large gene panel and subsequently diagnostic trio exome sequencing (ES) was carried out with no significant findings. However, reanalysis of the ES data one year later on a research basis revealed compound heterozygous variants in a novel candidate gene. Three other families with biallelic variants in this gene and a similar phenotype were identified through the 'Matchmaker Exchange' platform. In conclusion, we have identified a new muscle disease associated gene in a girl with proximal muscle weakness.

http://dx.doi.org/10.1016/j.nmd.2020.08.329

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Introme identifies non-canonical splice-altering variants in neuromuscular patients resulting in multiple new genetic diagnoses

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Genetic variants that impact pre-mRNA splicing can result in aberrant protein production and disease. Most diagnostic bioinformatic pipelines easily identify splice-altering variants within canonical splice acceptor and donor sites. However, non-canonical splice variants are missed by most pipelines. To address this area of need we developed Introme, a bioinformatic tool designed to identify both canonical and non-canonical splice-altering variants. Introme uses machine learning to integrate predictions from multiple splice detection tools (SpliceAI, MMSplice, dbscSNV, Branchpointer, SPIDEX & ESEFinder), allele frequency and conservation to evaluate the likelihood of a splice-altering impact. We systematically curated 906 functionally validated splice-altering variants and 565 variants with no splicing impact from the literature. Eighty percent of these variants were used to optimise a machine learning classifier. The remaining 20% of variants were used to test performance. Introme outperformed all previous splice variant detection tools (area under the receiver operating characteristic curve (AUC): 0.96), including SpliceAI (AUC 0.93) and MMSplice (AUC 0.81). Using Introme, we were able to identify 15 non-canonical splice-altering variants in a cohort of genetically unresolved neuromuscular patients. This included one nonsense variant which had an additional previously unrecognised splicing impact that appears to have reduced the severity the presenting clinical phenotype. The discovery of these additional splice-altering variants has resulted in a newly confirmed genetic diagnosis in multiple patients. Introme has also identified 3606 ClinVar-reported variants of uncertain significance in neuromuscular disease genes that are likely to have a significant impact on splicing. Introme is a powerful new splice variant detection tool which promises to significantly enhance our ability to detect diagnostically relevant splice-altering variants in neuromuscular patients.

http://dx.doi.org/10.1016/j.nmd.2020.08.330

REGISTRIES, CARE, QUALITY OF LIFE, MANAGEMENT OF NMD

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Cardiac involvement in Duchenne and Becker muscular dystrophy

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Duchenne muscular dystrophy (DMD) is a neuromuscular disease associated with progressive cardiac dysfunction. In this study we compared findings of heart rate variability (HRV), electrocardiographic (ECG) and echocardiographic (Echo) parameters of children with Duchenne and Becker muscular dystrophy (BMD) compared with healthy controls. It is aimed to determine the early markers of cardiac involvement. Twenty-six genetically confirmed boys with DMD&BMD, and 44 age-matched controls were recruited. ECG, Echo and HRV measurements of healthy controls who applied for routine sport licence examination and patients were retrospectively evaluated. ECG parameters were altered in the patients as compared to healthy controls, while there was no significant difference in Echo values. Following parameters were reduced in patients; RR($p<0,001$), V1RS ($p<0,01$). Heart rate was significantly higher in the DMD&BMD group ($p<0,05$). Compared to ambulatory patients, nonambulatory ones had lower SDNN, SDANN, SDNN index, rMSSD and pNNSO measurements ($p<0,05$). In this study we showed significant alterations in ECG and HRV in DMD compared to healthy controls of similar age. Electrical abnormalities may be the earliest manifestation of the histopathological process leading to the development of cardiac dysfunction.

http://dx.doi.org/10.1016/j.nmd.2020.08.331

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Novel and more sensitive criteria for identifying chronic respiratory failure in progressive neuromuscular disease

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In conditions with progressive respiratory muscle weakness the end stage is chronic respiratory failure. This is defined as the point at which the respiratory system is no longer able to both inhale the oxygen that the metabolic demands of the body requires and also to remove the carbon dioxide that the metabolic processes of the body produces. This is evaluated on nocturnal polysomnogram (sleep) study with monitoring of respiratory effort, oxygenation and capnography. The standard interpretation is based on American Society of Sleep Medicine (ASSM) guidelines using criteria for hypercarbia defined in patients with normal respiratory muscle strength (CO_2 > 50 mmHg for > 20% sleep). As such the threshold for hypercapnia and is higher than it should be, which can lead to a delay in diagnosing respiratory failure and initiating ventilatory support. Using the DELPHI process 15 pediatric pulmonologists with expertise in management of patients with neuromuscular disease, 9 of whom have additional expertise in sleep medicine, answered two rounds of questions from which consensus was reached on new criteria for identifying respiratory failure. Three criteria for respiratory failure were identified using both capnography and oxygenation data. CO_2: (1) CO_2 > 45 mmHg for > 25% of sleep, (2) 10 mmHg increase in CO_2 above sleep baseline for > 2% of sleep, and (3) CO_2 > 50 mmHg for >2% sleep or 5 minutes continuously. SpO_2: (1) mean SpO_2 < 94%, (2) SpO_2 < 90% for > 2% sleep, or (3) SpO_2 < 90% for > 5 minutes continuously. DISCUSSION: These new criteria for identifying respiratory failure using criteria based on CO_2 or SpO_2 allow for identification of respiratory failure at a level lower level pdf abnormal gas exchange dysfunction than the standard ASSM criteria. This allows not only for earlier identification of respiratory failure, but also for identifying respiratory failure from one of a variety of different patterns: persistent mild deficiency and shorter more severe deficiency. These criteria allow the sensitivity to identify respiratory failure earlier in progression than in with current guidelines, which allows for starting ventilatory assistance earlier in disease progression and can improve patient comfort and quality of life. These criteria are currently being validated more broadly using retrospective and prospective data.

http://dx.doi.org/10.1016/j.nmd.2020.08.332
