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Learning disabilities in neuromuscular disorders: a springboard for adult life

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Although the presence of cognitive deficits in Duchenne muscular dystrophy or myotonic dystrophy DM1 is well established in view of brain-specific expression of affected muscle proteins, in other neuromuscular disorders, such as congenital myopathies and limb-girdle muscular dystrophies, cognitive profiles are poorly defined. Also, there are limited characterization of the cognitive profile of children with congenital muscular dystrophies, notwithstanding the presence of cerebral abnormality in some forms, and in spinal muscular atrophies, with the exception of distal spinal muscular atrophy (such as the DYN1CH1-associated form).

Starting from the Duchenne muscular dystrophy, which may be considered a kind of paradigm for the co-occurrence of learning disabilities in the contest of a progressive muscular involvement, the findings of neuropsychological (or cognitive) dysfunctions in several forms of neuromuscular diseases will be examined and reviewed.

Key words: learning disasbility, DMD, CMD, CM, SMA-LED

Introduction

Several studies have suggested the presence of central nervous system involvement, manifesting as cognitive deficits or psychiatric problems, in neuromuscular disorders (NMD) (1, 2); however, few data are still known about subtle "not optimal" functions that, especially in a developing prospective, can impact cognitive and learning abilities (3).

It is well recognized indeed that learning disabilities can affect an individual's life beyond academics and can impact relationships with family, friends and in the workplace (4). On the other hand, in adults with NMD, quality of life and well-being are frequently restricted (5). Therefore, early identification of cognitive weakness in children with NMD is imperative to set psychological interventions and consequently improve quality of adult life.

The aim of the present work is to review the studies investigating the occurrence of neuropsychological deficits in children with NMD and their impact on later learning skills and academic achievement.

Duchenne muscular dystrophy

Over the past few decades there has been increasing attention to neurodevelopmental dysfunction in Duchenne muscular dystrophy (DMD), on the other hands research in cognition, learning, and behavior in Becker muscular dystrophy (BMD) is even scarcer, being limited to only few study (6, 7). Boys with DMD display distinct cognitive profiles and also exhibit neurobehavioral comorbidities, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders, and obsessive-compulsive disorder (8-12). Several studies have reported a non-progressive lower IQ in DMD boys compared to controls (1, 13), with about 30% having cognitive impairment, repeatedly been associated with mutations affecting brain specific isoforms of dystrophin (2, 14-20). Below-average reading performances have also been reported (21), and difficulty mastering academic material is a frequent concern during the primary years for this boys (22-24). Academic difficulties may be due to specific learning disabilities such as dyslexia or other cognitive deficits, such as impaired working memory (23). In a previous study we confirmed a high incidence of literacy prob-

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lems in boys with DMD showing a profile less severe than, but qualitatively similar to, Italian children with developmental dyslexia (DD) (3). Both DMD and DD boys showed specific difficulties in reading and writing words and reduced rapid automatized naming speed, a measure highly related to reading speed. Moreover, the boys with DMD and the subgroup of dyslexic children with a previous language delay showed additional deficits in phonological processing. In a more recent study, analyzing in a larger DMD population high order level cognitive skills, Executive Functions (EF), it has been shown that the neuropsychological profile is characterized by impairments in problem solving, inhibition and working memory, necessary to plan and direct goal oriented behavior in novel and complex tasks (25). It is well known that these processing problems could interfere with learning basic skills, such as reading, writing or math and psychological health in general (26).

Although difficulties in EF may be overlooked by parents and teachers because they are not disruptive, problems with planning, organization, initiation and self-evaluation may become more evident when boys progress through the grades and more and more independence is expected in their work. Moreover, as young men with DMD grow older, and expectations for responsibility increase, problems with short-term memory and EF can interfere with their ability to keep track of, and efficiently complete assignments and projects.

Further studies need to early identify preschool antecedents of cognitive and learning difficulties in DMD in order to better understand their causal relationships and to plan interventions aimed to empower functional strengths and weakness.

Myotonic dystrophy

Since the original descriptions of myotonic dystrophy type 1 (DM1), there have been numerous observations of decreased mental capabilities in these patients (27). From 10% to 24% of DM1 individuals show mental retardation, particularly those affected by the congenital form (28, 29). Studies on children with DM1 demonstrated that lower IQs correlate with longer expansions, mainly related to maternal inheritance and age of onset of symptoms (30, 31) although does not correlate with the neuromuscular impairment and the severity of disease. Nevertheless, patients with the childhood form of DM1 can have an IQ scores similar to those of the normal population, but show learning disabilities correlated to impairment in EF, visual perception, constructional ability and visual memory (32), more specifically in visuospatial recall and in both short and long-term components of verbal memory (33). Moreover, children and adolescents affected by the childhood type of DM1 presented prominent signs of psychopathology, most frequently an attention deficit with hyperactivity disorder and anxiety disorder (ADHD) (33-36).

Personality and behavioral disturbances, that could have cascade effects on cognitive functioning, are also well documented in the adult form: myotonic dystrophy present an homogeneous personality profile, with statistically significant differences for avoidance, obsessive-compulsive, passive-aggressive, emotional deficits and schizotypic traits. Nevertheless the depressive symptoms may arise from the emotional reaction to a disease, causing physical restrictions and disabilities (37).

These observations, also supported by neurofunctional studies (38, 39), suggest that patients affected by myotonic dystrophy, regardless of the form, may have striking inter-correlated cognitive and psychiatric features. Thus, it may be considered that an intervention on both behavioral and cognitive level may be useful to avoid psychosocial maladjustment.

Congenital muscular dystrophies and Limb-girdle muscular dystrophies

The congenital muscular dystrophies (CMD) encompass as a group, great clinical and genetic heterogeneity (40-42).

The degree of muscular and/or CNS involvement is variable within a spectrum from severe “floppy” infant syndrome with cerebral and cerebellar malformation and white matter abnormalities, to moderate motor delay and mild or moderate limb-girdle involvement during childhood, compatible with survival into adult life and relatively good quality of life. Alike, cognitive abilities can be severely affected, as in some forms of dystroglycanopathies (such as those with mutations in *POMT1, POMGnT1, LARGE...*) (43-45), or normal, as in the majority of affected individuals with merosin-deficiency (46-48).

Also the new and less characterized forms recently reported, such as *SYNE1*-related CMD (49), and *CHKB*-related muscle disease could be characterized by severe intellectual disability (50). We recently observed a CMD patient with a *TMEM5*-related dystroglycanopathy presenting with a mild muscular phenotype resembling a limb girdle muscle dystrophy (LGMD), in which the neuropsychological assessment revealed a moderate mental delay with low verbal skills and slight deficits in attention, short term working memory, and problem solving (51). The remaining forms of LGMD have usually normal cognitive abilities and low self-esteem and feelings of sadness and culpability as the only defined psy-

chopathlogical characteristics (52). Probably because of their heterogeneity and severity, there are no studies investigating more in deepth possible cognitive impairment or subtle learning deficits.

Congenital myopathies

Congenital myopathies are considered disorders restricted to the skeletal muscle, with few exceptions: anecdotally have been in fact described patient with structure myopathy, developmental delay, and, cerebellar deficits without any radiological sign of cerebral or cerebellar malformation (53, 54), or epileptic seizures and cerebral abnormalities (55). Considering that both cases have not a specific molecular definition and in view of the wide spectrum of genotype that could be related to some histological findings, the diagnosis of congenital myopathy could be questioned.

However, our own, as yet unpublished, observations suggest that patients with congenital myopathy, experience fatigability not only during motor skills but also during cognitive works. To support an involvement of cognitive process in congenital myopathy or in such neuromuscular disorders where fatigability is part of the framework (i.e metabolic myopathies or congenital myastenic syndrome), we recall a study on adolescent chronic fatigue syndrome (CFS), defined as persisting or relapsing fatigue of more than 3 months' duration, conduct in Norway, which reported that more than 80% of individuals with CFS complain cognitive problems concerning executive functions. Moreover, this study demonstrates that adolescents with chronic fatigue, perform worse than healthy control on measures of processing speed, working memory, verbal learning and cognitive inhibition response time, but not on cognitive flexibility or delayed recall. Group differences remained largely unaffected when adjusted for symptoms of depression, anxiety traits and sleep problems. According to parents' observations, their children with chronic fatigue have more problems with everyday EF as expected (56).

We suggests to take into consideration the reports of cognitive fatigability, and to systematically annotate this finding, to evaluate subtle cognitive dysfunction in such patients.

Spinal muscular atrophy and distal spinal muscular atrophy

Children with SMA are universally considered as "normal in intellect" or even "brighter than average" and this is a clear distinction if compared to DMD boys (57).

This clinical impression was subsequently confirmed in specific studies showing that SMA children are often more intelligent than healthy controls of the same age and from the same environment, or, than patients with the same degree of motor disabilities (57, 58). Moreover, academic skills required in verbal components of intelligence tests are most developed in patients with SMA, suggesting that these children develop effective and useful strategies to compensate for their physical handicap by the acquisition of cognitive skills and knowledge (59, 60).

However, although this figure still seems to be true for patients with SMA II or III, it has been questioned for patients with SMA I, where not-sufficient long term studies can be achieved due to their reduced life expectancy.

Moreover, while not considering the forms of SMA in which the involvement of the central nervous system is known (i.e. SMA-PME), it has been recently described patients with other form of progressive spinal muscular atrophy with congenital or early-onset, identified as autosomal dominant or sporadic congenital spinal muscular atrophy with lower extremity predominance (SMA-LED) (61) that could be associated with severe intellectual disability or learning difficulties (62-65).

Scoto et al., recently reported a large cohort of children and adults affected by SMA-LED due to *DYNC1H1* mutations, in which one-third presented mild to moderate cognitive impairment and/or behavioral comorbidities consistent with ADHD traits, not appear to be related to the severity of the motor impairment (66).

In continuum of the spectrum, there are the adult onset progressive spinal muscular atrophies (PMA) that has been recently documented to have a cognitive dysfunction similar to those found in patients with motor neuron disease with upper motor neuron (UMN) involvement such as ALS (67). In this study, executive dysfunction and verbal recall deficits were demonstrated in PMA similar but less extensive than in ALS and no differences in depression or anxiety scores have been found between PMA patients with and without cognitive impairment.

Also in Spinal and bulbar muscular atrophy (SBMA), Kennedy's disease, another form of PMA, it was recently found minor cognitive disturbance in the working memory (digit span backward task), verbal fluency category (single letter fluency task) and memory storage capacity (digit span forward task) (68).

These data suggest some continuity between the broad spectrum of SMA (SMA, SMA-LED, SMA-PME) and PMA, also for the brain involvement. Knowledge of this dyadic relationship between muscle and brain is important as, with prolonged life expectancy, these learning and neurobehavioral disorders may have growing impact and may be highly debilitating.

Conclusions

Literature on cognitive and learning skills in NMD diseases is still scarce but the existing studies converge in lighting impairments in the EF domain and three main scenario may be suggested. In several NMD diseases, as supported by neurofunctional studies, abilities in control interference, updating information in memory and cognitive flexibility may represent the "core cognitive difficulties". In other forms, as in many other neurodevelopmental disorders, the cognitive profile may be characterized by subtle working memory and/or processing speed difficulties. Finally in some NMD it may be the case that motor dysfunctions and psychological co-variables play a major role on higher order cognitive dyfunctions, as executive functions may often due to impaired lower-order functioning, such as perception, information processing and response speed. Although further studies are needed to better understand causal relationships in the different NMD conditions, not optimal cognitive functioning seem a common feature of all (Fig. 1).

Meanwhile the findings so far described suggest to explore cognitive functions to understand the extramotor involvement and the heterogeneity within the NMD spectrum and target the correct interventions for the school, in view of the negative impact that school failure can play on quality of life, school attendance and social and family functioning.

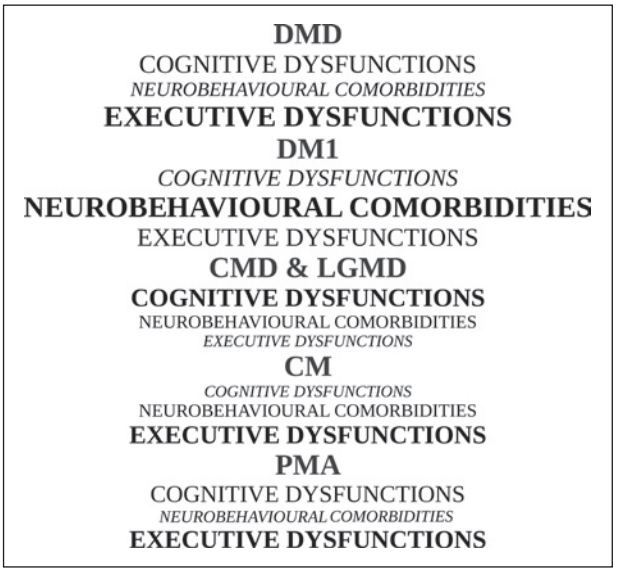

Figure 1. Schematic representation of cognitive dysfunctions in NMD.

References

1. Bresolin N, Castelli E, Comi GP, et al. Cognitive impairment in Duchenne muscular dystrophy. Neuromuscul Disord 1994;4:359-69.
2. D'Angelo MG, Bresolin N. Cognitive impairment in neuromuscular disorders. Muscle Nerve 2006;34:16-33.
3. Astrea G, Pecini C, Gasperini F, et al. Reading impairment in Duchenne muscular dystrophy: a pilot study to investigate similarities and differences with developmental dyslexia. Res Dev Disabil 2015;45-46:168-77.
4. Barbiero CI, Lonciari I, Montico M, et al. The submerged dyslexia iceberg: how many school children are not diagnosed? Results from an Italian study. PLoS One 2012;7:e48082.
5. Walklet E, Muse K, Meyrick J, et al. Do psychosocial interventions improve quality of life and wellbeing in adults with neuromuscular disorders? A Systematic review and narrative synthesis. J Neuromuscul Dis 2016;3:347-62.
6. Young HK, Barton BA, Waisbren S, et al. Cognitive and psychological profile of males with Becker muscular dystrophy. J Child Neurol 2008;23:155-62.
7. Banihani R, Smile S, Yoon G, et al. Cognitive and neurobehavioral profile in boys with duchenne muscular dystrophy. J Child Neurol 2015;30:1472-82.
8. Leibowitz D, Dubowitz V. Intellect and behavior in Duchenne muscular dystrophy. Dev Med Child Neurol 1981;23:577-90.
9. Hinton VJ, Cyrulnik SE, Fee RJ, et al. Association of autistic spectrum disorders with dystrophinopathies. Pediatr Neurol 2009;41: 339-46.
10. Pane M, Lombardo ME, Alfieri P, et al. Attention deficit hyperactivity disorder and cognitive function in Duchenne muscular dystrophy: phenotype-genotype correlation. J Pediatr 2012;161:705-9.
11. Snow WM, Anderson JE, Jakobson LS. Neuropsychological and neurobehavioral functioning in Duchenne muscular dystrophy: a review. Neurosci Biobehav Rev 2013;37:743-52.
12. Ricotti V, Mandy WP, Scoto M, et al. Neurodevelopmental, emotional, and behavioural problems in Duchenne muscular dystrophy in relation to underlying dystrophin gene mutations. Dev Med Child Neurol 2016;58:77-84.
13. Cotton S, Voudouris NJ, Greenwood KM. Intelligence and Duchenne muscular dystrophy: full-scale, verbal, and performance intelligence quotients. Dev Med Child Neurol 2001;43:497-501.
14. Al-Qudah AA, Kobayashi J, Chuang S, et al. Etiology of intellectual impairment in Duchenne muscular dystrophy. Pediatr Neurol 1990;6:57-9.
15. Moizard MP, Billard C, Toutain A, et al. Are Dp71 and Dp140 brain dystrophin isoforms related to cognitive impairment in Duchenne muscular dystrophy? Am J Med Genet 1998;80:32-41.
16. Austin RC, Morris GE, Howard PL, et al. Expression and synthesis of alternatively spliced variants of Dp71 in adult human brain. Neuromuscul Disord 2000;10:187-93.
17. Felisari G, Martinelli Boneschi F, Bardoni A, et al. Loss of Dp140 dystrophin and intellectual impairment in Duchenne dystrophy. Neurology 2000;55:559-64.
18. Mehler MF. Brain dystrophin, neurogenetics and mental retardation. Brain Res Rev 2000;32:277-307.
19. Taylor PJ, Betts GA, Maroulis S, et al. Dystrophin gene mutation location and the risk of cognitive impairment in Duchenne muscular dystrophy. PLoS One 2010;20;5:e8803.
20. Magri F, Govoni A, D'Angelo MG, et al. Genotype and phenotype characterization in a large dystrophinopathic cohort with extended follow-up. J Neurol 2011;258:1610-23.

21. Dorman C, Desnoyers Hurley A, D'Avignon J. Language and learning disorders in older boys with Duchenne muscular dystrophy. Devel Med Child Neurol 1988;30:316-27.
22. Billard C, Gillet P, Barthez MA, et al. Reading ability and processing in Duchenne muscular dystrophy and spinal muscular atrophy. Devel Med Child Neurol 1998;40:12-20.
23. Hinton VJ, DeVivo DC, Nereo NE, et al. Poor verbal working memory across intellectual level in boys with Duchenne dystrophy. Neurology 2000;54:2127-32.
24. Lorusso ML, Civati F, Molteni M, et al. Specific profiles of neurocognitive and reading functions in a sample of 42 Italian boys with Duchenne Muscular Dystrophy. Child Neuropsychol 2013;19:350-69.
25. Battini R, Chieffo D, Bulgheroni S, et al. Neuropsychological profile in Duchenne Muscular Dystrophy boys without intellectual disability. Dev Med Child Neurol (submitted).
26. Moffitt TE, Arsenault L, Belsky D, et al. A gradient of childhood self-control predicts health, wealth, and public safety. Proc Natl Acad Sci U S A 2011;15;108:2693-8.
27. Harper PS. Myotonic dystrophy. 2nd edition. Philadelphia: Saunders 1989.
28. Bird TD, Follett C, Griep E. Cognitive and personality functions in myotonic muscular dystrophy. J Neurol Neurosurg Psychiatry 1983;46:971-80.
29. Modoni A, Silvestri G, Pomponi MG, et al. Characterization of the pattern of cognitive impairment in myotonic dystrophy type 1. Arch Neurol 2004;61:1943-7.
30. Perini GI, Menegazzo E, Ermani M, et al. Cognitive impairment and (CTG)n expansion in myotonic dystrophy patients. Biol Psychiatry 1999;46:425-31.
31. Endo A, Motonaga K, Arahata K, et al. Developmental expression of myotonic dystrophy protein kinase in brain and its relevance to clinical phenotype. Acta Neuropathol 2000;100:513-20.
32. Meola G, Sansone V, Perani D, et al. Executive dysfunction and avoidant personality trait in myotonic dystrophy type 1 (DM-1) and in proximal myo-tonic myopathy (PROMM/DM-2). Neuromuscul Disord 2003;13:813-21.
33. Douniol M, Jacquette A, Cohen D, et al. Psychiatric and cognitive phenotype of childhood myotonic dystrophy type 1. Dev Med Child Neurol 2012;54:905-11.
34. Brumback RA. Disturbed personality and psychosocial adjustment in myotonic dystrophy: relationship to intellectual/cognitive function and underlying affective disorder (depression). Psychol Rep 1987;60:783-96.
35. Bungener C, Jouvent R, Delaporte C. Psychopathological and emotional deficits in myotonic dystrophy. J Neurol Neurosurg Psychiatry 1998;65:353-6.
36. Delaporte C. Personality patterns in patients with myotonic dystrophy. Arch Neurol 1998;55:635-40.
37. Goossens E, Steyaert J, De Die-Smulders C, et al. Emotional and behavioral profile and child psychiatric diagnosis in the childhood type of myotonic dystrophy. Genet Couns 2000;11:317-7.
38. Huber SJ, Kissel JT, Shuttleworth EC, et al. Magnetic resonance imaging and clinical correlates of intellectual impairment in myotonic dystrophy. Arch Neurol 1989;46:536-40.
39. Chang L, Anderson T, Migneco OA, et al. Cerebral abnormalities in myotonic dystrophy. Cerebral blood flow, magnetic resonance imaging, and neuropsychological tests. Arch Neurol 1993;50:917-23.
40. Mercuri E, Sewry C, Brown SC, Muntoni F. Congenital muscular dystrophies. Semin Pediatr Neurol 2002;9:120-31.
41. Mercuri E, Muntoni F. Muscular dystrophies. Lancet 2013;381:845-60.
42. Bönnemann CG, Wang CH, Quijano-Roy S, et al. Diagnostic approach to the congenital muscular dystrophies. Neuromuscul Disord 2014;24:289-311.
43. Beltran-Valero de Bernabe D, Currier S, Steinbrecher A, et al. Mutations in the O-mannosyltransferase gene POMT1 give rise to the severe neuronal migration disorder Walker–Warburg syndrome. Am J Hum Genet 2002;71:1033-43.
44. Longman C, Brockington M, Torelli S, et al. Mutations in the human LARGE gene cause MDC1D, a novel form of congenital muscular dystrophy with severe mental retardation and abnormal glycosylation of alpha-dystroglycan. Hum Mol Genet 2003;12:2853-61.
45. Chiyonobu T, Sasaki J, Nagai Y, et al. Effects of fukutin deficiency in the developing mouse brain. Neuromuscul Disord 2005;15:416-26.
46. Jones KJ, Morgan G, Johnston H, et al. The expanding phenotype of laminin alpha2 chain (merosin) abnormalities: case series and review. J Med Genet 2001;38:649-57.
47. Bönnemann CG. Congenital muscular dystrophy. In: Squire LR, ed. Encyclopedia of Neuroscience. Vol. 3. Oxford, UK: Oxford Academic Press 2009, pp. 67-74.
48. Geranmayeh F, Clement E, Feng LH, et al. Genotype-phenotype correlation in a large population of muscular dystrophy patients with LAMA2 mutations. Neuromuscul Disord 2010;20:241-50.
49. Voit T, Cirak S, Abraham S, et al. Congenital muscular dystrophy with adducted thumbs, mental retardation, cerebellar hypoplasia, and cataracts is caused by mutation of Enaptin (Nesprin-1): the third nuclear envelopathy with muscular dystrophy. Taormina, Italy: 12th International Congress of the World Muscle Society, 2007.
50. Mitsuhashi S, Ohkuma A, Talim B, et al. A congenital muscular dystrophy with mitochondrial structural abnormalities caused by defective de novo phosphatidylcholine biosynthesis. Am J Hum Genet 2011;88:845-51.
51. Astrea G, Pezzini I, Picillo E, et al. TMEM5-associated dystroglycanopathy presenting with CMD and mild limb-girdle muscle involvement. Neuromuscul Disord 2016;26:459-61.
52. Miladi N, Bourguignon JP, Hentati F. Cognitive and psycho-logical profile of a Tunisian population of limb girdle muscular dystrophy. Neuromuscul Disord 1999;9:352-4.
53. Chudley AE, Rozdilsky B, Houston CS, et al. Multicore disease in sibs with severe mental retardation, short stature, facial anomalies, hypoplasia of the pituitary fossa, and hypogonadotrophic hypogonadism. Am J Med Genet 1985;20:145-58.
54. Kim JJ, Armstrong DD, Fishman MA. Multicore myopathy, microcephaly, aganglionosis, and short stature. J Child Neurol 1994;9:275-7.
55. Ryan MM, Schnell C, Strickland CD, et al. Nemaline myopathy: a clinical study of 143 cases. Ann Neurol 2001;50:312-20.
56. Sulheim D, Fagermoen E, Sivertsen ØS, et al. Cognitive dysfunction in adolescents with chronic fatigue: a cross-sectional study. Arch Dis Child 2015;100:838-44.
57. Billard C, Gillet P, Signoret JL, et al. Cognitive functions in Duchenne muscular: a reappraisal and comparison with spinal muscular atrophy. Neuromuscul Disord 1992;2:371-8.
58. Ogasawara A. Downward shift in IQ in persons with Duchenne muscular dystrophy compared to those with spinal muscular atrophy. Am J Ment Retard 1989;93:544-7.
59. Carter GT, Abresch RT, Fowler WM Jr, et al. Profiles of neuromuscular diseases. Spinal muscular atrophy. Am J Phys Med Rehabil 1995;74(suppl):S150-9.

60. Von Gontard A, Zerres K, Backes M, et al. Intelligence and cognitive function in children and adolescents with spinal muscular atrophy. Neuromuscul Disord 2002;12:130-6.
61. Deng HX, Klein CJ, Yan J, et al. Scapuloperoneal spinal muscular atrophy and CMT2C are allelic disorders caused by alterations in TRPV4. Nat Genet 2010;42:165-9.
62. Vissers LE, de Ligt J, Gilissen C, et al. A de novo paradigm for mental retardation. Nat Genet 2010;42:1109-12.
63. Weedon MN, Hastings R, Caswell R, et al. Exome sequencing identifies a DYNC1H1 mutation in a large pedigree with dominant axonal Charcot-Marie-Tooth disease. Am J Hum Genet 2011;89:308-12.
64. Willemsen MH, Vissers LE, Willemsen MA, et al. Mutations in DYNC1H1 cause severe intellectual disability with neuronal migration defects. J Med Genet 2012;49:179-83.
65. Fiorillo C, Moro F, Julie Yi, et al. Novel dynein DYNC1H1 neck and motor domain mutations link distal SMA and abnormal cortical development. Hum Mutat. 2014; 35:298-302.
66. Scoto M, Rossor AM, Harms MB, et al. Novel mutations expand the clinical spectrum of DYNC1H1-associated spinal muscular atrophy. Neurology 2015;17;84:668-79.
67. Raaphorst J, de Visser M, van Tol MJ, et al. Cognitive dysfunction in lower motor neuron disease: executive and memory deficits in progressive muscular atrophy. J Neurol Neurosurg Psychiatry 2011;82:170-5.
68. Kasper E, Wegrzyn M, Marx I, et al. Minor cognitive disturbances in X-linked spinal and bulbar muscular atrophy, Kennedy's disease. Amyotroph Lateral Scler Frontotemporal Degener 2014;15:15-20.