European Journal of Human Genetics (2015) 23, doi:10.1038/ejhg.2015.12

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CLINICAL UTILITY GENE CARD UPDATE

Clinical utility gene card for: Nemaline myopathy - update 2015

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European Journal of Human Genetics (2015) **23,** doi:10.1038/ejhg.2015.12; published online 25 February 2015

Update to: *European Journal of Human Genetics* (2012) **20**, doi:10.1038/ejhg.2012.70; published online 18 April 2012

1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Nemaline myopathy (NEM1—NEM10).

Includes nemaline myopathy with excess thin filaments/actin aggregates; nemaline myopathy with cores; nemaline myopathy with intranuclear rods; and Amish nemaline myopathy.

1.2 OMIM# of the disease

NEM1 - 609284; NEM2 - 256030; NEM3 - 161800; NEM4 - 609285; NEM5 - 605355; NEM6 - 609273; NEM7 - 610687; NEM8 - 615348; NEM9 - 615731; NEM10 - 616165.

1.3 Name of the analysed genes or DNA/chromosome segments

Slow muscle α-tropomyosin (TPM3) - NEM1.
Nebulin (NEB) - NEM2.
Skeletal muscle α-actin (ACTA1) - NEM3.
β-tropomyosin (TPM2) - NEM4.
Slow muscle troponin-T (TNNT1) - NEM5.
Kelch-repeat and BTB (POZ) Domain containing 13 (KBTBD13) - NEM6.
Skeletal muscle cofilin (CFL2) - NEM7.
KELCH-like 40 (KLHL40) - NEM8.
KELCH-like 41 (KLHL41) - NEM9.
Leiomodin 3 (LMOD3) - NEM10.

1.4 OMIM# of the gene(s)

TPM3 = *191030; NEB = *161650; ACTA1 = *102610; TPM2 = *190990; TNNT1 = *191041; KBTBD13 = *613727; CFL2 = *601443; KLHL40 = *615340; KLHL41 = *607701; LMOD3 = *616112.

1.5 Mutational spectrum

TPM3: mainly dominant, missense variants;[1,2] however, some recessive variants have been described.[3,4] A 1 bp recessive deletion occurs as a founder variant in the Turkish population.[5]

NEB: all of the over 140 variants identified to date are recessive and the patients are usually compound heterozygous. The majority of the variants are either frameshift or nonsense variants, but also missense variants, and point variants and deletions affecting splice sites are known.[6,7] An in-frame deletion of exon 55 is present in the Ashkenazi Jewish population at a carrier frequency of ~1 in 108.[8] Some patients present with a distal myopathy, with their skeletal muscle biopsies containing nemaline bodies, both nemaline bodies and cores, or no nemaline bodies.[9,10] Rare cases of core-rod myopathy with generalised muscle weakness may also be caused by *NEB* variants.[11]

ACTA1: over 200 different variants identified, with the majority causing nemaline myopathy, or nemaline myopathy with other features (eg cores, actin aggregates, intranuclear rods and zebra bodies).[12] Of these, most variants are dominant, missense, and have arisen *de novo*.[13] About 10% are recessive variants. Most recessive variants are genetic or functional null variants[13] but recently recessive *ACTA1* disease with retention of skeletal muscle actin expression was described in a family presenting with a rigid spine syndrome.[14] Dominant inheritance is less common, and only seen in families with a milder phenotype.[13] Somatic mosaicism is possible with dominant variants.[15] Some variants can cause hypercontractile skeletal muscle rather than weakness.[16]

TPM2: Two heterozygous, dominant missense variants causing nemaline myopathy are known.[17] Also a homozygous null variant in a patient with nemaline and Escobar syndrome,[18] and a dominant heterozygous variant in a mother with nemaline myopathy and her daughter with cap myopathy[19] have been identified. A K7del variant was identified in a family with nemaline bodies and minicores (presenting as a distal myopathy), and also in four unrelated families with distal arthrogryposis type 7 with nemaline bodies.[20] The K7del variant also causes progressive skeletal muscle contractures, most probably because of the hypercontractility caused by the mutant protein in nemaline myopathy and/or core-rod myopathy patients.[21]

TNNT1: a recessive nonsense founder variant is present in the Old Order Amish population. This produces a characteristic progressive nemaline myopathy with tremors and contractures.[22] *TNNT1* variants have now been identified outside the Amish population.[23]

KBTBD13: three dominant missense variants have been identified.[24] There was phenotypic variability, with some variant carriers exhibiting only very mild proximal leg weakness on targeted examination.

CFL2: homozygous missense variants have been identified in two families,[25,26] and a homozygous 4 bp deletion identified in another family.[27] The severity of the disease is greater in the family with the homozygous null variant.

KLHL40: homozygous or compound heterozygous variants (mainly missense, but also frameshift, splice site and nonsense variants) cause

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Received 30 July 2014; revised 16 December 2014; accepted 13 January 2015; published online 25 February 2015

severe autosomal recessive nemaline myopathy with prenatal onset of symptoms, including foetal akinesia or hypokinesia and contractures.[28] At birth, the children may have fractures, respiratory failure and severe swallowing difficulties.[28]

KLHL41: Recessive homozygous or compound heterozygous variants have been reported, with frameshift variants leading to a severe phenotype with neonatal death, and missense variants compatible with survival into late childhood or early adulthood.[29]

LMOD3: Recessive homozygous and compound heterozygous variants cause severe, usually lethal nemaline myopathy.[30]

Regularly updated variant databases exist for *ACTA1*, *CFL2, KBTBD13, KLHL40, NEB*, *TNNT1, TPM2* and *TPM3* at the Leiden Muscular Dystrophy pages (http://www.dmd.nl).

1.6 Analytical methods

The main analytical method has been bi-directional Sanger sequencing of the entire coding region of the individual genes. If the family structure is amenable, linkage analysis for *NEB* may be useful to pre-screen, because of the large size of the gene. Next-generation sequencing now allows for simultaneous analysis of all genes in a patient through whole-exome sequencing. Alternatively sub-exomic sequencing using a panel of selected genes can include all known nemaline myopathy genes.[31] It should be noted however that limitations of current high throughput sequencing technologies prevent complete screening of all exons in all genes (eg, regions of genes that have high GC content or are repetitive).

1.7 Analytical validation

Variants should be confirmed by resequencing using a fresh dilution of genomic DNA. Putative variants identified through next-generation sequencing methods should be confirmed by Sanger sequencing. Special care should be taken in interpreting missense variants in the nebulin gene as affecting function.[10]

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)

For the most part, the frequency of the disease is unknown. In Finland, the birth incidence has been estimated to be 0.02 per 1000 live births.[32] *De novo* dominant variants in *ACTA1* and recessive variants in *NEB* are the most common causes of NEM.[33,34]

1.9 If applicable, prevalence in the ethnic group of investigated person

Recessive founder variants are known to exist in particular genes in specific populations: *TNNT1* in the Amish;[22] *NEB* in the Ashkenazi Jewish[8] and in the Finnish population.[10] *ACTA1* in the Pakistani community in England, and in French and Spanish Roma;[13] *TPM3* in the Turkish population;[5] and *KLHL40* in Japanese persons.[28] These specific cases aside, no clear differences in prevalence rates are known between different ethnic groups.

1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☒	☐
C. Risk assessment in relatives	☒	☐
D. Prenatal	☒	☐

Comment: requests for predictive testing are not common because of the early onset of the disease, but may be offered in families with childhood or late-onset forms of the disease.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives B: False positives	C: False negative D: True negative
	Present	Absent		
Test				
Positive	A	B	Sensitivity:	A/(A+C)
			Specificity:	D/(D+B)
Negative	C	D	Positive predictive value:	A/(A+B)
			Negative predictive value:	D/(C+D)

2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)

100%.

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)

100%.

2.3 Clinical Sensitivity
(proportion of positive tests if the disease is present)

The clinical sensitivity is dependent on factors such as age, inheritance pattern and additional clinical features. Because of the genetic heterogeneity, and particularly the difficulty of screening *NEB*, full screening of all known nemaline myopathy genes has historically not been possible. However, next-generation technologies are now getting closer to such screening. If full screening were to be undertaken, it may be estimated that ~75% of patients would have a variant(s) identified.[6,13]

2.4 Clinical specificity
(proportion of negative tests if the disease is not present)

The clinical specificity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case. Probably 100%.

2.5 Positive clinical predictive value (life time risk of developing the disease if the test is positive)

Nearly 100%. Potential incomplete penetrance has been suggested for certain *ACTA1* variants[35] and a very mild phenotype can be associated with some *KBTBD13* variants.[24]

2.6 Negative clinical predictive value (probability of not developing the disease if the test is negative)

Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:

Approximately 100%.

Index case in that family had not been tested:

No predictive tests are usually performed in such cases.

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: The tested person is clinically affected
(To be answered if in 1.10 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

No.	☐	
	(continue with 3.1.4)	
Yes,	☒	
	Clinically	☒
	Imaging	☒ MRI imaging of muscles may be able to direct variant testing, especially in uncertain/ambiguous cases.
	Endoscopy	☐
	Biochemistry	☐
	Electrophysiology	☐
	Other (please describe)	☒ Histopathology, including electron microscopy of skeletal muscle. Besides 'pure' nemaline myopathy, variants in the known NEM genes have also been described in association with other congenital myopathies, which clinically can appear similar to nemaline myopathy. Pathologically, some patients have features in addition to nemaline bodies (eg, cores[36]). Patients with variants in the NEM genes may also have a myopathy without nemaline bodies, and may be diagnosed as having actin myopathy (*ACTA1*[15]), intranuclear rod myopathy (*ACTA1* eg[37]), congenital fibre type disproportion (OMIM #255310; *ACTA1*;[38] *TPM3*[39,40]), cap disease (*ACTA1*;[41] *TPM2*;[42,43] *TPM3*[44,45]) and distal myopathy (NEB[46,47]). Variants in *TPM2* and other nemaline myopathy genes can also cause distal arthrogryposis.[48] Variants in other genes may also be associated with these additional histological features, for example nemaline myopathy with cores with variants in *RYR1*,[49] and congenital fibre type disproportion with *RYR1*[50] or *SEPN1*[51] variants. Variants in *TPM2* or *TPM3* can cause congenital myopathies with neuromuscular transmission defects that can benefit from treatment with anticholinesterase therapy.[52,53] Nemaline bodies can also be identified as secondary features, such as in mitochondrial disorders[54] and HIV.[55]

3.1.2 Describe the burden of alternative diagnostic methods to the patient

Nemaline myopathy is both a clinical and, significantly, a histopathological/electron microscopic diagnosis. Therefore, a thorough assessment including a detailed evaluation of clinical and pathological features should be performed along with genetic testing. As such, histopathology and electron microscopy are not diagnostic alternatives, rather prerequisites to genetic testing. Nevertheless, muscle biopsy is an invasive procedure, and appropriate histological and electron microscopic examination requires proximity to a specialised laboratory set up.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

Not applicable.

3.1.4 Will disease management be influenced by the result of a genetic test?

No	☐	
Yes	☒	
	Therapy (please describe)	Presently, the treatment of patients is based on symptom management, which would occur regardless of the genetic diagnosis. However, an accurate genetic diagnosis will undoubtedly be extremely important for any causal therapies once they are developed.
	Prognosis (please describe)	Varied, as nemaline myopathy can be severe (foetal or congenital presentation) through to mild,[56] even with variants in the same gene. For example, most patients with *ACTA1* variants affecting function die within their first year of life, whilst some patients have a milder phenotype compatible with survival into adulthood.[13] However, even severely affected patients who survive the first year of life may improve functionally in subsequent years. Patients with the recessive *TNNTI* variant die within 2 years of birth. The 'typical' subtype of nemaline myopathy is considered non-progressive.
	Management (please describe)	Supportive—mechanical ventilation; night-time ventilation; naso-gastric feeding; mobility aids; physiotherapy, occupationVirual and speech therapy; surgery for scoliosis where needed. Cardiomyopathy is not normally present; however, some instances have been reported with *ACTA1* variants. As an example, see ref. 57. Genetic testing is required for verifying the diagnosis and determining the mode of inheritance, which serves as a basis for genetic counselling.

3.2 Predictive Setting: The tested person is clinically unaffected but carries an increased risk based on family history
(To be answered if in 1.10 'B' was marked)

Predictive testing is usually only applicable for the milder versions of nemaline myopathy, as most often the disease presents before, at or shortly after birth.

3.2.1 Will the result of a genetic test influence lifestyle and prevention?

If the test result is positive (please describe)	The positive test result may influence lifestyle choices for later onset of disease, for example deciding which career to pursue (eg, an office job compared with something physical), whether to travel at a young age when mobility is not affected compared with later in life and whether to have a house on one level as opposed to over multiple stories (eg, the latter would involve climbing lots of stairs which might become problematic). Respiratory precautions and self-monitoring for sleep-related breathing problems may be advised. A positive test will greatly influence prevention, through the availability of prenatal or pre-implantation diagnosis for the family.

If the test result is negative (please describe)	A negative test result does not rule out the diagnosis of nemaline myopathy because of the possibility of currently unidentified causative genes or pathogenic variants not being identified in, for example, regions of *NEB* that are difficult to sequence and/or map in next-generation sequencing.[31] In this situation, prevention through genetic counselling is less informed. In terms of predictive testing, a negative result may influence lifestyle choices as indicated above, such as choice of occupation.

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)?
Not applicable.

3.3 Genetic risk assessment in family members of a diseased person
(To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
Yes, if a variant/s is identified.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Genetic testing would still most likely be performed for other family members, however, other tests such as skeletal muscle biopsy might be prevented.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Yes, but owing to very early disease onset in most cases, it is infrequently encountered.

3.4 Prenatal diagnosis
(To be answered if in 1.10 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?
Yes. In cases where dominant *de novo* variants have been identified in an affected child, genetic counselling may be difficult, as the recurrence risk is between 0 and 25% because of the possibility of gonadal mosaicism. However, prenatal genetic testing of an at-risk pregnancy is accurate.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe).

Yes, particularly if a variant/s are identified. An accurate genetic diagnosis often ends a lengthy diagnostic odyssey for the patient and their family, removing the psychological effects of an absent disease, and can sometimes influence possible prognosis. An accurate genetic diagnosis can crucially indicate the mode of inheritance and underpins genetic counselling, including options such as prenatal and pre-implantation testing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by EuroGentest2 (Unit 2: 'Genetic testing as part of health care'), a Coordination Action under FP7 (Grant Agreement Number 261469), the European Society of Human Genetics, an Australian National Health and Medical Research Council (NH&MRC) Fellowship APP1002147 and an Australian Research Council (ARC) Future Fellowship FT100100734.

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