CLINICAL UTILITY GENE CARDS

Clinical utility gene card for: 3M syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

3M syndrome (gloomy face syndrome, dolichospondylic dysplasia).

1.2 OMIM of the disease

273750.

1.3 Name of the analysed genes or DNA/chromosome segments

CUL7 and OBSL1.

1.4 OMIM of the gene(s)

609577 (CUL7) and 610991 (OBSL1).

1.5 Mutational spectrum

CUL7: predominance of null mutations (nonsense and splice site but missense also frequent). A total of 50% of CUL7 mutations are located in the cullin domain critical for anchoring the ROC1 protein; the others are located throughout the gene).

Major gene involved in 75% of 3M cases

OBSL1: mutations within the first eight exons affecting all known isoforms; predominance of loss-of-function mutations.

Prevalent mutation p.T245fsX40 identified in 12/23 families with OBSL1 mutations.

A few subset of patients (<10%) have no mutation in CUL7 or OBSL1, supporting the involvement of a third gene.

1.6 Analytical methods

CUL7: genomic DNA extracted from peripheral blood. A total of 23 primers to amplify 25 coding exons, purifying with exonuclease I and sequencing.

OBSL1: genomic DNA extracted from peripheral blood. Intronic primers for each of the 22 exons. Polymerase chain reaction amplification and sequencing.

1.7 Analytical validation

CUL7: microsatellites analysis of the locus (6p21.1) in consanguineous families.

Demonstration that the 3M-associated CUL7 nonsense and missense mutations R1445X and H1464P, respectively, render CUL7 deficient in recruiting ROC1, leading to impaired ubiquitination.

OBSL1: microsatellites analysis of the locus (2q35-36.1) in consanguineous families.

Mutations induce nonsense-mediated decay. Knockdown of OBSL1 in HEK293 cells show the role of this gene in the maintenance of normal levels of CUL7.

Abnormal IGFBP2 and IGFBP5 mRNA levels in two patients with OBSL1 mutations, suggesting that OBSL1 modulates the expression of insulin-like growth factor binding proteins.

1.8 Estimated frequency of the disease

(incidence at birth ('birth prevalence') or population prevalence)

Rare. <100 cases reported in the literature since 1975.

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

Not applicable.

1.10 Diagnostic setting

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

Comment:

2. TEST CHARACTERISTICS

Genotype or disease		A: true positives	C: false negatives
		B: false positives	D: true negatives
		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)

Not applicable.

2.2 Analytical specificity

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

Not applicable.

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2.3 Clinical sensitivity

(proportion of positive tests if the disease is present)

The clinical sensitivity can be dependant 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.

In all, 80–90% due to genetic heterogeneity.

2.4 Clinical specificity

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

The clinical specificity can be dependant 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.

(Not applicable).

2.5 Positive clinical predictive value

(lifetime risk to develop the disease if the test is positive)

The disease is antenatally present (not applicable).

2.6 Negative clinical predictive value

(probability not to develop the disease if the test is negative)

Assume an increased risk on the basis of family history for a non-affected person. Allelic and locus heterogeneity may need to be considered (not applicable).

Index case in that family had been tested:

Index case in that family had not been tested:

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: The tested person is clinically affected

(To be answered if in 1.10 'A' was marked)

Molecular testing for 3M syndrome is clinically indicated if the following suggestive features are present:

Typical facial features including relatively large head, triangular face, hypoplastic midface, full eyebrows, fleshy nose tip, long philtrum, prominent mouth and lips, and pointed chin. Facial appearance varies among affected individuals.

Additional features, such as a short broad neck, prominent trapezii, deformed sternum, short thorax, square shoulders, winged scapulae, hyperlordosis, dislocated hips, and short fifth fingers.

Prominent heels and loose joints.

Male hypogonadism and hypospadias.

Radiographic findings, which may not be present until after 2 years of age, include:

Long bones are slender with diaphyseal constriction and flared metaphyses, which seem to be the main radiologic features of 3M syndrome. Increased radiolucency is unusual.¹⁰ The metacarpal index, used to document slender long bones, is usually high.

Vertebral bodies are tall with reduced anterior-posterior and transverse diameter, especially in the lumbar region. Foreshortening of the vertebral bodies becomes more apparent with increasing age. Calculation of the vertebral index at different ages reveals that the vertebral index of L1 is a useful tool to document 3M syndrome, although tall vertebrae are a nonspecific finding that may be secondary to scoliosis or hypotonia. Anterior wedging of thoracic vertebral bodies, irregular upper and lower endplates, thoracic kyphoscoliosis, and spina bifida occulta are also features of 3M syndrome.

Pelvic bones are small, especially the pubis and the ischium. The iliac wings are flared and the obturator foramina are small, although the latter may be positional. The femoral necks can be short.

Thorax is broad with slender and horizontal ribs.

Bone age is slightly delayed.

Other findings include dolichocephaly, flattened coronal suture, narrowed intraorbital distance, elbow dysplasia, shortened ulna, pseudo-epiphyses of the second metacarpal bone, clinodactyly of the little fingers, dislocated hips, and prominent talus.

DIFFERENTIAL DIAGNOSIS

Russel–Silver syndrome: characterized by intrauterine growth retardation, accompanied by postnatal growth deficiency. The birth weight of affected individuals is typically two or more SD below the mean, and postnatal growth two or more SD below the mean for length or height. Affected individuals typically have proportionately short stature, normal head circumference, typical facial features, and limb-length asymmetry that may result from hemihypotrophy, with diminished growth of the *affected* side. About 10% of individuals with Russel–Silver syndrome will have maternal disomy for chromosome 7 and up to another 50% will have abnormal methylation at the imprinting control centre on chromosome 11 (H19 and IGF-1). Body asymmetry is not usually seen in 3M syndrome. The radiographic findings of 3M are not seen in Russel–Silver syndrome. Russel–Silver syndrome is sporadic, whereas 3M is autosomal recessively inherited.

Dubowitz syndrome: includes characteristic facial appearance (small face with sloping forehead, broad nasal bridge, shallow supraorbital ridge, broad nasal tip, short palpebral fissures, telecanthus, ptosis, dysplastic ears), microcephaly, mental deficiency, and infantile eczema, as well as prenatal and postnatal growth deficiency. Although Dubowitz syndrome is also inherited in an autosomal recessive manner, it can be differentiated from 3M by the presence of typical facial features, eczema, microcephaly, and developmental delay.

Mulibrey nanism: includes prenatal and postnatal growth deficiency with relatively large hands, triangular faces with frontal bossing and depressed nasal bridge, small tongue, yellowish dots on the fundus, and pericardial constriction. Elongated sella turcica and cystic bone changes of the tibiae are also seen. These findings differentiate it from 3M syndrome clinically and radiographically. The gene responsible for this disorder is TRIM37. Mulibrey nanism is inherited in an autosomal recessive manner.

Fetal alcohol syndrome: Microcephaly decreased subcutaneous fat, hirsutism, nail hypoplasia, facial appearance, and mental retardation with significant behavioural problems are the primary features, and these allow differentiation from 3M syndrome. A history of antenatal exposure to excess alcohol is also present.

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

No (continue with 3.1.4)	☐
Yes	☒
Clinically	☒
Imaging	☒
Endoscopy	☐
Biochemistry	☐
Electrophysiology	☐
Other (please describe)	☐

3.1.2 Describe the burden of alternative diagnostic methods to the patient

Repeated X-rays.

Endocrine investigations and follow-up.

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

The only way to definitely rule out differential diagnoses would be the genetic test.

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

No ☐
Yes ☒

Therapy (please describe): Surgical bone lengthening. Endocrine treatment (hormone therapy for hypogonadism in males, growth hormone but usually not efficient).

Prognosis (please describe): Short stature (−5 to −6 s.d.)

Management (please describe): Regular and frequent growth follow-up, occupational therapy, support group, schooling.

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).

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

If the test result is positive (please describe):

If the test result is negative (please describe):

Yes for management of the growth retardation and prevention of recurrence if positive.

Yes for pursuing analysis towards differential diagnoses.

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)?

Identical options if clinical features consistent with the diagnosis.

3.3 Genetic risk assessment in family members of a diseased person

(To be answered if in 1.10 'C' was marked).

Siblings if consanguinity, parents for prenatal diagnosis, and their relatives depending on their risk of having affected children.

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?

Yes, as there is no need to search for other similar conditions.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

No.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?

No.

3.4 Prenatal diagnosis

(To be answered if in 2.10 'D' was marked).

Prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. The 3M syndrome should also be considered if ultrasound examination reveals significant slowing of long bone growth.

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnostic?

Yes.

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, for management, treatment, prenatal diagnosis, and genetic counselling. Other differential diagnoses can then be ruled out. It is generally reassuringly informative that the disease has been identified.^{1–11}

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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- 1 Avela K, Lipsanen-Nyman M, Idanheimo N *et al*: Gene encoding a new RING-B-box-Coiled-coil protein is mutated in mulibrey nanism. *Nat Genet* 2000; **25**: 298–301.
- 2 Elliott AM, Graham JM, Curry CJ, Pal T, Rimoin DL, Lachman RS: Spectrum of dolichospondylic dysplasia: two new patients with distinctive findings. *Am J Med Gene* 2002; **113**: 351–361.
- 3 Hanson D, Murray PG, Sud A *et al*: The primordial growth disorder 3-M syndrome connects ubiquitination to the cytoskeletal adaptor OBSL1. *Am J Hum Genet* 2009; **84**: 801–806.
- 4 Huber C, Dias-Santagata D, Glaser A *et al*: Identification of mutations in CUL7 in 3-M syndrome. *Nat Genet* 2005; **37**: 1119–1124.
- 5 Huber C, Delezoide A-L, Guimiot F *et al*: A large-scale mutation search reveals genetic heterogeneity in 3M syndrome. *Eur J Hum Genet* 2009; **17**: 395–400.
- 6 Huber C, Fradin M, Edouard T *et al*: OBSL1 mutations in 3-M syndrome are associated with a modulation of IGFBP2 and IGFBP5 expression levels. *Hum Mut* 2010; **31**: 20–26.
- 7 Marik I, Marikova O, Kuklik M, Zemkova D, Kozlowski K: 3-M syndrome in two sisters. *J Paediatr Child Health* 2002; **38**: 419–422.
- 8 Meo F, Pinto V, D'Addario V: 3-M syndrome: a prenatal ultrasonographic diagnosis. *Prenat Diagn* 2000; **20**: 921–923.
- 9 Temtamy SA, Aglan MS, Ashour AM, Ramzy MI, Hosny LA, Mostafa MI: 3-M syndrome: a report of three Egyptian cases with review of the literature. *Clin Dysmorphol* 2006; **15**: 55–64.
- 10 van der Wal G, Otten BJ, Brunner HG, van der Burgt I: 3-M syndrome: description of six new patients with review of the literature. *Clin Dysmorphol* 2001; **10**: 241–252.
- 11 Maksimova N, Hara K, Miyashita A *et al*: Clinical, molecular and histopathological features of short stature syndrome with novel CUL7 mutation in Yakuts: new population isolate in Asia. *J Med Genet* 2007; **44**: 772–778.