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NLM Citation: Irving M, Holder-Espinasse M. Three M Syndrome. 2002 Mar 25 [Updated 2019 Feb 7]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Three M Syndrome

Synonyms: 3-M Syndrome, 3M Syndrome

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Created: March 25, 2002; Updated: February 7, 2019.

Summary

Clinical characteristics

Three M syndrome is characterized by severe pre- and postnatal growth deficiency (final height 5-6 SD below the mean; i.e., 120-130 cm), characteristic facies, and normal intelligence. Additional features of three M syndrome include short broad neck, prominent trapezii, deformed sternum, short thorax, square shoulders, winged scapulae, hyperlordosis, short fifth fingers, prominent heels, and loose joints. Males with three M syndrome have hypogonadism and occasionally hypospadias.

Diagnosis/testing

The diagnosis of three M syndrome is established in a proband with characteristic clinical and radiographic features. Identification of biallelic pathogenic variants in *CCDC8*, *CUL7*, or *OBSL1* can establish the diagnosis if clinical and radiographic features are inconclusive.

Management

Treatment of manifestations: Surgical bone lengthening may be an option. Adaptive aids for people with short stature are appropriate. Significant joint laxity should prompt orthopedic evaluation and measures to control the development of arthritis. Males with three M syndrome should be referred for endocrinologic evaluation regarding gonadal function at puberty.

Surveillance: Monitoring of growth every 6-12 months on standard growth charts, with special attention to growth velocity.

Genetic counseling

Three M syndrome is inherited in an autosomal recessive manner. Each sib of a proband with three M syndrome has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased

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risk are possible for families in which the pathogenic variants have been identified in an affected family member. Prenatal ultrasound examination reveals slowing of growth of all long bones.

Diagnosis

Suggestive Findings

Three M syndrome **should be suspected** in a proband with a combination of the following clinical and radiographic features.

Clinical features

- **Short stature** of prenatal onset [Lugli et al 2016]. Typical height is -5.0 SDS (standard deviation score) [Shapiro et al 2017].
- **Facial features.** Relatively large head, dolichocephaly, triangular face, midface retrusion, thick eyebrows, fleshy nasal tip, long philtrum, full lips, and pointed chin. Facial appearance varies among affected individuals [van der Wal et al 2001, Marik et al 2002].
- **Musculoskeletal features.** Short broad neck, prominent trapezii, deformed sternum, short thorax, square shoulders, winged scapulae, thoracic kyphoscoliosis, hyperlordosis, spina bifida occulta, clinodactyly of the fifth fingers, generalized or isolated joint hypermobility, prominent heels, and pes planus
- **Genitourinary anomalies in males.** Hypogonadism and hypospadias
- **Intelligence.** Usually unaffected

Radiographic features are subtle and may include the following (most often present after age 2 years):

- **Long bones** are slender with diaphyseal constriction and flared metaphyses. The femoral necks can be short.
- **Vertebral bodies** are tall with reduced anterior-posterior and transverse diameter (especially in the lumbar region), anterior wedging of the thoracic vertebral bodies, and irregular upper and lower endplates; thoracic kyphoscoliosis; spina bifida occulta.
- **Thorax** is relatively broad with slender, horizontal ribs.
- **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.
- **Bone age** is slightly delayed. There is a high metacarpal index.
- **Other findings** include dolichocephaly, flattened coronal suture, narrowed intraorbital distance, elbow dysplasia, shortened ulna, pseudoepiphyses of the second metacarpal bone, dislocated hips, and prominent talus.

Establishing the Diagnosis

The diagnosis of three M syndrome **is established** in a proband with prenatal-onset persistent growth deficiency and the characteristic clinical and radiographic features described in Suggestive Findings. Identification of biallelic pathogenic variants in one of the genes listed in Table 1 can confirm the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (concurrent or serial single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of three M syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas

those in whom the diagnosis of three M syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of three M syndrome, molecular genetic testing approaches can include concurrent or serial single-gene testing) or use of a **multigene panel**.

- **Serial single-gene testing.** Sequence analysis detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis of *CUL7* first, followed by sequence analysis of *OBSL1*, then *CCDC8*. If only one or no pathogenic variant is found, gene-targeted deletion/duplication analysis of *CCDC8*, *CUL7*, and/or *OBSL1* can be performed next to detect intragenic deletions or duplications.
- **A multigene panel** that includes *CCDC8*, *CUL7*, *OBSL1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of three M syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Three M Syndrome

Gene [1, 2]	Proportion of Three M Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
CCDC8	<5% [6]	100% [6]	None reported [6]
CUL7	77.5% [7]	100% [7]	None reported [7]
OBSL1	16% [7, 8]	100% [7]	None reported [7, 8]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of Three M Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
Unknown [9]	>1.5%		

1. Genes are listed alphabetically.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Hanson et al [2011]
7. Huber et al [2009], Huber et al [2011]
8. Hanson et al [2009]
9. Pathogenic variants in *CCDC8, CUL7,* and *OBSL1* do not account for 100% of 3-M syndrome, it is postulated that mutation of other genes (potentially members of the same pathway) may be involved [Huber et al 2011].

Clinical Characteristics

Clinical Description

Growth deficiency. The most striking feature of three M syndrome is the severe intrauterine growth restriction. Birth length is 40-42 cm, whereas the head size is normal for gestational age. Catch-up growth does not occur; final height is 5-6 standard deviations below the mean (i.e., 120-130 cm) [van der Wal et al 2001], resulting in proportionate short stature.

Although most children with three M syndrome are evaluated for growth hormone (GH) deficiency, only one individual has been reported with an incomplete response to GH stimulation, suggesting partial deficiency of GH [Miller et al 1975]. Several individuals with short stature have been treated with exogenous GH without positive result [Miller et al 1975]. One report suggested that high-dosage GH treatment may be effective in three M syndrome [van der Wal et al 2001]. No obvious demonstration of growth hormone efficacy has been published to date [Huber et al 2011, Meazza et al 2013].

Facial features. Infants with three M syndrome have a relatively large head, triangular face, midface retrusion, thick eyebrows, fleshy nose tip, long philtrum, thick lips, and pointed chin. Facial appearance varies among affected individuals [van der Wal et al 2001, Marik et al 2002] and changes over time, with the pointed chin, long philtrum, and triangular face becoming more pronounced.

Musculoskeletal features present by early childhood variably include short broad neck, prominent trapezii, deformed sternum, short thorax, square shoulders, winged scapulae, and hyperlordosis. Short fifth fingers, prominent heels, and loose joints are reported. Developmental dysplasia of the hips has been reported with delayed diagnosis [Badina et al 2011].

Radiographic features

- The **long bones** are slender with diaphyseal constriction and flared metaphyses; these appear to be the main radiologic features of three M syndrome. Increased radiolucency is unusual [van der Wal et al 2001]. The metacarpal index, used to document slender long bones, is usually high.
- The **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 three M 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 three M syndrome.

- **Thorax** is broad with slender and horizontal ribs.
- **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.
- **Bone age** is slightly delayed.
- **Other findings** include dolichocephaly, flattened coronal suture, narrowed intraorbital distance, elbow dysplasia, shortened ulna, pseudoepiphyses of the second metacarpal bone, clinodactyly of the fifth fingers, dislocated hips, and prominent talus.

Genitourinary anomalies in males may include gonadal dysfunction and subfertility or infertility as documented by high FSH levels, low testicular volume, and abnormal semen analysis [van der Wal et al 2001]. Hypospadias has been seen in a few males with three M syndrome. Note: Female gonadal function appears normal.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been reported to date.

Nomenclature

The name "three M" derives from the initials of the authors who first described the condition. Three M syndrome may also be referred to as Le Merrer syndrome or Yakut short stature syndrome.

Dolichospondylic dysplasia, described by Elliott et al [2002], is probably the same as three M syndrome. Findings include normal facial appearance except for epicanthal folds and ocular hypertelorism, borderline intellectual disability, and radiographic findings similar to three M syndrome.

Gloomy face syndrome is likely the same condition as three M. In one report, the facial features and the mode of inheritance are identical; however, radiologic abnormalities were absent. No follow-up information is available; the characteristic radiologic findings could have appeared later [Le Merrer et al 1991].

Prevalence

Three M syndrome is rare. The prevalence is not known; approximately 100 affected individuals have been reported in the literature since the first published report in 1975 [Miller et al 1975].

Genetically Related (Allelic) Disorders

Three M syndrome is the only disorder known to be associated with pathogenic variants in *CCDC8*, *CUL7*, or *OBSL1*.

Differential Diagnosis

Intrauterine growth retardation is a nonspecific finding that occurs in approximately 0.17% of all live-born children. Three M syndrome must be distinguished from other forms of intrauterine growth retardation-malformation syndromes, including the following (see Table 2).

Table 2. Disorders to Consider in the Differential Diagnosis of Three M Syndrome

Disorder	Gene(s)	MOI	Clinical Features of This Disorder	
			Overlapping w/3-M syndrome	Distinguishing from 3-M syndrome
Silver-Russell syndrome (SRS)	See footnote 1	Simplex	IUGR, postnatal growth deficiency	• SRS often shows limb length asymmetry. • Characteristic radiologic features of 3-M are absent.
Dubowitz syndrome (OMIM 223370)	Unknown	AR	IUGR	• Microcephaly • Eczema • Characteristic facial features (small face w/ sloping forehead, broad nasal bridge, shallow supraorbital ridge, broad nasal tip, short palpebral fissures, telecanthus, ptosis, dysplastic ears) • Intellectual disability
Mulibrey nanism (OMIM 253250)	*TRIM37*	AR	IUGR	• IUGR often less severe than in infants w/3-M • Characteristic facial features (high forehead, pseudo-hydrocephalic skull configuration)
Fetal alcohol syndrome	NA	NA	IUGR	• Microcephaly • ↓ subcutaneous fat • Hirsutism • Nail hypoplasia • Characteristic facial features • Intellectual disability

AR = autosomal recessive; IUGR = intrauterine growth restriction; MOI = mode of inheritance
1. Hypomethylation of the paternal imprinting center 1 (IC1) of chromosome 11p15.5 is identified in 35%-50% of individuals with SRS. About 10% of individuals with SRS have maternal uniparental disomy for chromosome 7 (UPD7).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with three M syndrome, the following evaluations are recommended if they have not already been completed:

- Physical examination to assess for hip dislocation, joint mobility, and kyphoscoliosis
- Referral to a pediatric endocrinologist for:
  - Evaluation for growth hormone deficiency (uncommon) at the time of diagnosis
  - Assessment of gonadal function in pubertal males by physical examination and serum concentrations of FSH, LH, and testosterone
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

The predominant management issues are ultimate adult stature and growth:

- Significant joint laxity should prompt orthopedic evaluation and measures to control the development of arthritis.
- Surgical bone lengthening may be an option for some.
- Adaptive aids for people with short stature are appropriate.

- Males with three M syndrome should be referred for endocrinologic evaluation for assessment of gonadal function at puberty.
- Treatment with growth hormone is indicated in the presence of documented growth hormone (GH) deficiency, but treatment of children with normal serum concentration of growth hormone is experimental. GH treatment should be carried out in a center with experience in managing growth disorders.

  Note: Several individuals with short stature have been treated with exogenous GH without positive result [Miller et al 1975]. One report suggested that high-dosage GH treatment may be effective in three M syndrome [van der Wal et al 2001]. No obvious demonstration of growth hormone efficiency has been published to date [Huber et al 2011].

Surveillance

Monitor growth every six to 12 months on standard growth charts with special attention to growth velocity.

Monitor for hip dislocation in infancy, especially if walking is delayed.

Examine back annually for kyphoscoliosis.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic younger sibs of a proband and at-risk relatives in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Physical examination and skeletal survey for the characteristic clinical and radiographic features if the pathogenic variants in the family are not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Management of pregnancy for affected women is the same as that for women with other forms of dwarfism or small stature, which is mainly to reduce the risk of premature birth.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Three M syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *CCDC8*, *CUL7*, or *OBSL1* pathogenic variant).
- Heterozygotes (carriers) are typically asymptomatic, although some reports have suggested that characteristic facies, a prominent talus, and slender long bones may be observed in carriers.

Sibs of a proband

- At conception, each sib of a proband has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are typically asymptomatic, although some reports have suggested that characteristic facies, a prominent talus, and slender long bones may be observed in carriers.

Offspring of a proband

- The offspring of an individual with three M syndrome are obligate heterozygotes (carriers) for a *CCDC8*, *CUL7*, or *OBSL1* pathogenic variant.
- Females with three M syndrome are fertile.
- Males with three M syndrome may be infertile.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CCDC8*, *CUL7*, or *OBSL1* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *CCDC8*, *CUL7*, or *OBSL1* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the three M syndrome-causing pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Ultrasound examination. The diagnosis of three M syndrome is rarely suspected during pregnancy, since intrauterine growth restriction is not specific, and the skeletal findings only appear after birth.

In one report of a child diagnosed with three M syndrome, measurement at 18 weeks' gestation showed femur and tibia lengths on the fifth centile and radius, ulna, and humerus lengths below the fifth centile. At 22 weeks' gestation, slowing of growth of all long bones was observed [Meo et al 2000].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Human Growth Foundation**
  hgfound.org
- **Little People of America**
  Phone: 888-LPA-2001; 714-368-3689
  Fax: 707-721-1896
  Email: info@lpaonline.org
  lpaonline.org
- **MAGIC Foundation**
  Phone: 630-836-8200
  Email: contactus@magicfoundation.org
  magicfoundation.org
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Three M Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CCDC8	19q13.32	Coiled-coil domain-containing protein 8		CCDC8	CCDC8

Table A. continued from previous page.

CUL7	6p21.1	Cullin-7	CUL7 database	CUL7	CUL7
OBSL1	2q35	Obscurin-like protein 1	OBSL1 database	OBSL1	OBSL1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Three M Syndrome (View All in OMIM)

273750	THREE M SYNDROME 1; 3M1
609577	CULLIN 7; CUL7
610991	OBSCURIN-LIKE 1; OBSL1
612921	THREE M SYNDROME 2; 3M2
614145	COILED-COIL DOMAIN-CONTAINING PROTEIN 8; CCDC8
614205	THREE M SYNDROME 3; 3M3

CCDC8

Gene structure. *CCDC8* comprises a single exon (NM_032040.4). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The three reported *CCDC8* frameshift variants are predicted to lead to the generation of a premature-termination codon [Hanson et al 2011, Al-Dosari et al 2012].

Normal gene product. *CCDC8* is a single-exon gene encoding coiled-coil domain-containing protein 8, a protein of 538 amino acids (NP_114429.2), with a coiled-coil domain located between residues 349-369 and 513-535 and an alanine-rich domain located between residues 299 and 471.

Abnormal gene product. Pathogenic variants are predicted to generate truncated CCD8 with subsequent loss of function. Neither would be expected to lead to nonsense-mediated decay [Hanson et al 2011].

CUL7

Gene structure. *CUL7* comprises 26 exons (NM_014780.3). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 60 distinct pathogenic variants have been identified [Huber et al 2005, Huber et al 2009] (see Table A, for variant databases). A novel homozygous c.4581dupT pathogenic variant in *CUL7* was found; it resulted in a frameshift and predicted a premature stop codon in members of the Yakut population with three M syndrome [Maksimova et al 2007]. One individual with three M syndrome had uniparental isodisomy for chromosome 6 [Huber et al 2009].

Table 3. *CUL7* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
c.4333C>T	p.Arg1445Ter	NM_014780.3 NP_055595.2
c.4391A>C	p.His1464Pro	
c.4581dupT (4582_4583insT)	p.Arg1528SerfsTer26 (Arg1528LeufsTer26)	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. *CUL7* encodes cullin-7, which comprises 1698 amino acids. Cullin-7 belongs to the cullin family, which is composed of structurally related proteins that share an evolutionarily conserved cullin domain. Cullin-7 assembles an E3 ubiquitin ligase complex containing Skp1, Fbx29 (also called Fbw8), and ROC1 and promotes ubiquitination. Cullin-7 uses its central region to interact with the Skp1-Fbx29 heterodimer [Huber et al 2005].

Abnormal gene product. *CUL7* nonsense variant p.Arg1445Ter and missense variant p.His1464Pro render cullin-7 deficient in recruiting ROC1, suggesting that impaired ubiquitination may have a role in the pathogenesis of intrauterine growth retardation in humans [Huber et al 2005].

OBSL1

Gene structure. *OBSL1* comprises 22 exons. Alternative splicing results in three splice forms that encode different protein isoforms. For a detailed summary of gene, alternative spliced transcripts, and protein information, see Table A, **Gene**.

Pathogenic variants. To date, all identified pathogenic variants have occurred in exons 1-6 and are either nonsense or frameshift.

Normal gene product. *OBSL1* encodes obscurin-like protein 1, which comprises three splice forms designated A, B, and C, containing 1896, 1401, and 1025 amino acids, respectively. Obscurin-like protein 1 is a putative cytoskeletal adaptor protein that acts with cullin-7 in a common cellular pathway. Obscurin is a muscle protein localized to sarcomeres implicated in cell signaling [Hanson et al 2009].

Abnormal gene product. All identified *OBSL1* pathogenic variants occurred in the first six exons; the majority are predicted to induce the nonsense-mediated decay pathway resulting in failure to produce obscurin-like protein 1. Furthermore, pathogenic variants near the N terminus lead to loss of all protein isoforms, explaining the clustering of pathogenic variants in this region of the gene [Hanson et al 2009].

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Chapter Notes

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* Robin Winter was Professor of Clinical Genetics and Dysmorphology at the Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust. He contributed nearly 300 papers to medical journals on a wide breadth of topics and was an editor of the journal *Clinical Dysmorphology* and co-author of the London Dysmorphology and Neurogenetics Databases. Professor Winter died January 10, 2004 after a brief illness.

Revision History

- 7 February 2019 (sw) Comprehensive update posted live
- 26 January 2012 (me) Comprehensive update posted live
- 30 September 2010 (cd) Revision: sequence analysis and prenatal testing available clinically for *CUL7* mutations. Mutations in *OBSL1* also cause 3-M syndrome.
- 30 March 2010 (me) Comprehensive update posted live
- 23 June 2006 (ca) Comprehensive update posted live
- 8 December 2005 (mhe) Revision: *CUL7* mutations associated with 3-M syndrome
- 11 May 2004 (me) Comprehensive update posted live
- 25 March 2002 (me) Review posted live
- 31 January 2002 (mhe) Original submission

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