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MBTPS1-Related Spondyloepimetaphyseal Dysplasia with Elevated Lysosomal Enzymes

Synonym: Spondyloepiphyseal Dysplasia, Kondo-Fu Type (SEDKF)

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Summary

Clinical characteristics

MBTPS1-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes (*MBTPS1*-SEMD) is characterized by postnatal-onset short stature, chest deformity (pectus carinatum or pectus excavatum), kyphosis and/or scoliosis, reduced bone density, inguinal hernia, protruding abdomen, cataracts, developmental delay, and dysmorphic facial features (prominent forehead, prominent cheekbones, retromicrognathia, wide mouth, and large, prominent ears). Additional features can include waddling or staggering gait, craniosynostosis, mild intellectual disability, and seizures. Imaging findings include diffuse osteopenia, copper-beaten appearance of the skull, dysplasia of multiple thoracolumbar vertebrae, long bones with small and irregular epiphyses and mildly enlarged and irregular metaphyses, hip dysplasia with small fragmented sclerotic femoral heads, and short metacarpals and metatarsals with small epiphyses. Increased concentration of multiple lysosomal hydrolase enzymes can be identified in plasma and dried blood spots.

Diagnosis/testing

The diagnosis of *MBTPS1*-SEMD is established in a proband with characteristic clinical and radiographic findings, elevated lysosomal hydrolase enzymes in plasma or dried blood spots, and biallelic pathogenic variants in *MBTPS1* identified by molecular genetic testing.

Management

Treatment of manifestations: Management of kyphoscoliosis, scoliosis, and hip dysplasia per orthopedist; vitamin D and calcium for reduced bone density; treatment of craniosynostosis per craniofacial specialist; surgical repair per surgeon and/or gastroenterologist for hernia; surgical removal of cataract per ophthalmologist; physical

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therapy to maximize mobility and reduce the risk for later-onset orthopedic complications; developmental and educational support.

Surveillance: Annual growth assessment, orthopedic evaluation, ophthalmological evaluation, and assessment of developmental progress and educational needs; clinical assessment for hernia as needed.

Agents/circumstances to avoid: In children with significant kyphoscoliosis, sports that place stress on the spine (e.g., heavy lifting, weight-bearing exercises) should be avoided.

Pregnancy management: Although no pregnancies have been reported in individuals with *MBTPS1*-SEMD, pregnancy and delivery may be complicated in individuals with significant short stature and skeletal dysplasia; delivery by cesarean section may be necessary.

Genetic counseling

MBTPS1-SEMD is inherited in autosomal recessive manner. If both parents are known to be heterozygous for an *MBTPS1* pathogenic variant, each sib of an affected individual has at conception 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. Once the *MBTPS1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

MBTPS1-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes (*MBTPS1*-SEMD) **should be suspected** in probands with the following clinical, laboratory, and imaging findings.

Clinical findings (See Figures 1 and 2.)

- Postnatal-onset short stature
- Kyphosis and/or scoliosis
- Inguinal hernia
- Protruding abdomen
- Cataracts (often congenital)
- Developmental delay (gross motor and/or speech)
- Dysmorphic facial features, including prominent forehead, prominent cheekbones, retromicrognathia, wide mouth, and large, prominent ears

Laboratory findings

- **Increased concentration** of multiple lysosomal hydrolase enzymes in **plasma** and **dried blood spots** including alpha-fucosidase, alpha-glucosidase, alpha-iduronidase, alpha-mannosidase, beta-glucuronidase, beta-hexosaminidase, and beta-mannosidase [Kondo et al 2018, Meyer et al 2020, Alotaibi et al 2022]
- **Increased activity** of lysosomal enzymes including alpha-N-acetylgalactosaminidase, alpha-N-acetylglucosaminidase, beta-glucuronidase, total beta-hexosaminidases, hexosaminidase A (MUGS substrate), and iduronate-2-sulfatase in **plasma**, but **normal activity in leukocytes** [Carvalho et al 2020]

Imaging findings [Kondo et al 2018, Carvalho et al 2020, Meyer et al 2020, Alotaibi et al 2022, Chen et al 2023, Yuan et al 2023] (See Figures 3, 4, 5, and 6.)

- Diffuse osteopenia
- Copper-beaten appearance of the skull

- Dysplasia of multiple thoracolumbar vertebrae: irregular cortex of the vertebrae (rough rather than smooth vertebral outline), end plate bone defects, ovoid lumbar vertebrae, and narrow intervertebral spaces [Carvalho et al 2020]
- Long bones with small and irregular epiphyses and mildly enlarged and irregular metaphyses; long bones may be short and bowed
- Significant hip dysplasia with small, fragmented sclerotic femoral heads
- Short metacarpals and metatarsals with small epiphyses [Carvalho et al 2020]

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *MBTPS1*-SEMD **is established** in a proband with suggestive clinical and radiographic findings, elevated lysosomal hydrolase enzymes in plasma or dried blood spots, and biallelic pathogenic (or likely pathogenic) variants in *MBTPS1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of biallelic *MBTPS1* variants of uncertain significance (or of one known *MBTPS1* pathogenic variant and one *MBTPS1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *MBTPS1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Typically, if only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder.

A skeletal dysplasia or lysosomal disorders / mucopolysaccharidoses multigene panel that includes *MBTPS1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition 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.

Figure 1. Craniofacial features of several children with *MBTPS1*-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes. Characteristic features include prominent forehead, prominent cheekbones, retromicrognathia, wide mouth, and large, prominent ears.

Reproduced with permission from Kondo et al [2018] (A); Carvalho et al [2020] (B); Meyer et al [2020] (C); Alotaibi et al [2022] (D); Chen et al [2023] (E); Yuan et al [2023] (F)

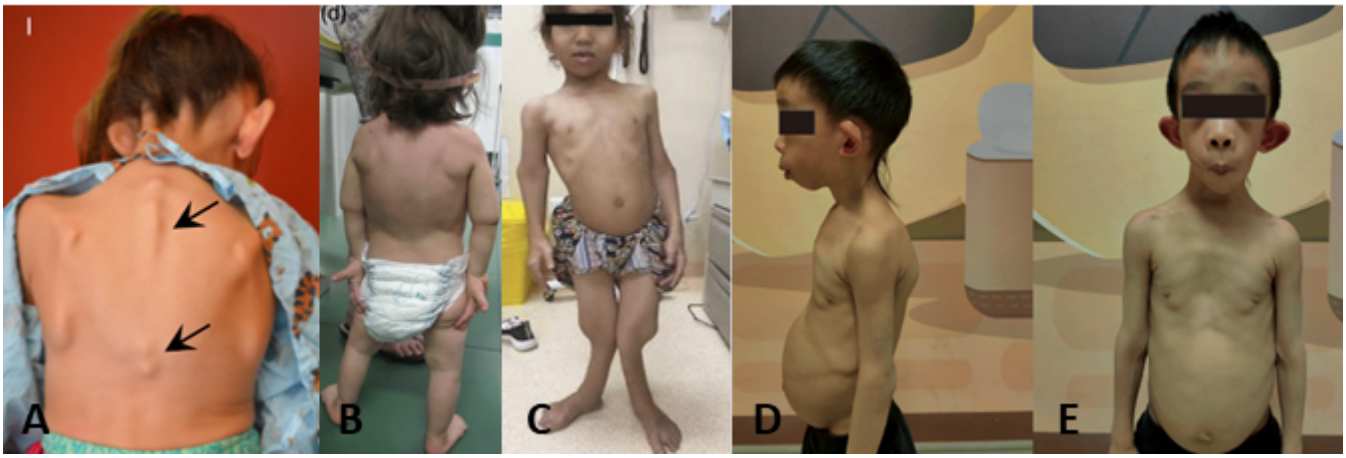

Figure 2. Clinical features of several children with *MBTPS1*-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes

A. Affected child at age six years with kyphoscoliosis (black arrows point to the prominent spinous processes)

B. Affected child at age 40 months with shortening of limbs and kyphoscoliosis

C. Affected child at age ten years with triangular face, prominent cheekbones, micrognathia, short neck, protruding abdomen, shortening of limbs, and genu valgum

D, E. Affected child at age six years with laterally protruding ears, retromicrognathia, sternal malformation, protruding abdomen, and kyphoscoliosis

Reproduced with permission from Kondo et al [2018] (A); Carvalho et al [2020] (B); Alotaibi et al [2022] (C); Chen et al [2023] (D, E)

Option 2

When the phenotype is indistinguishable from many other skeletal dysplasias, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **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.

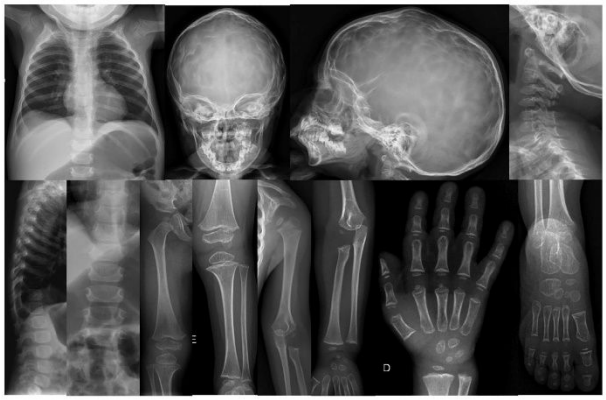

Figure 3. Radiographs of a child with *MBTPS1*-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes, age 37 months, with diffuse osteopenia; ovoid lumbar vertebral bodies; irregular aspect of cervical vertebral bodies, with mild reduction of vertebrae height; metaphyseal and epiphyseal irregularities of the long bones; mild metaphyseal enlargement; small epiphysis of the tubular bones; and copper-beaten skull.

Reproduced with permission from Carvalho et al [2020]

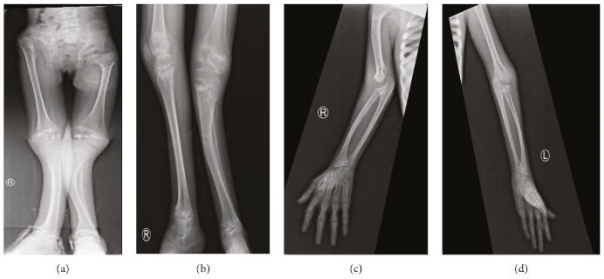

Figure 4. Radiographs of children with *MBTPS1*-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes showing diffuse osteopenia and metaphyseal sclerosis

A. Irregularities more pronounced in the femoral heads, coxa vara, right hip dislocation with external rotation of the lower limbs, and short tubular bones with bowing deformity of the left tibia

B. Left genu valgus and bowing deformity of the left tibia

C, D. Bowed right humerus and short metacarpals

Reproduced with permission from Alotaibi et al [2022]

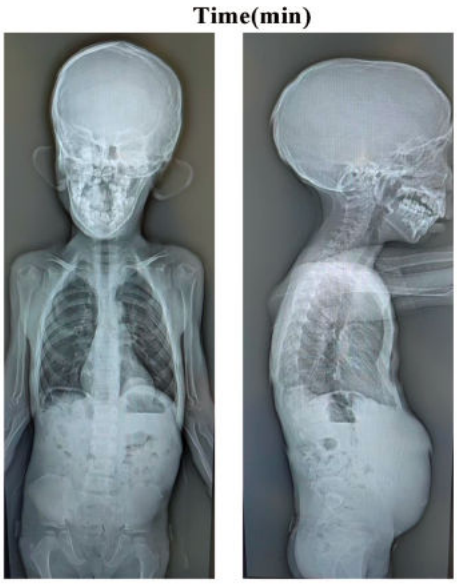

Figure 5. Skull and spine radiographs of child, age six years, with MBTPS1-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes. Straightened physiologic curvature of the cervical, thoracic, and lumbar spine. Irregular morphology and reduced bone density of the vertebral bodies, C2-C3 and C3-C4 intervertebral disc space narrowing, and bilateral shallow acetabulae.

Reproduced with permission from Chen et al [2022]

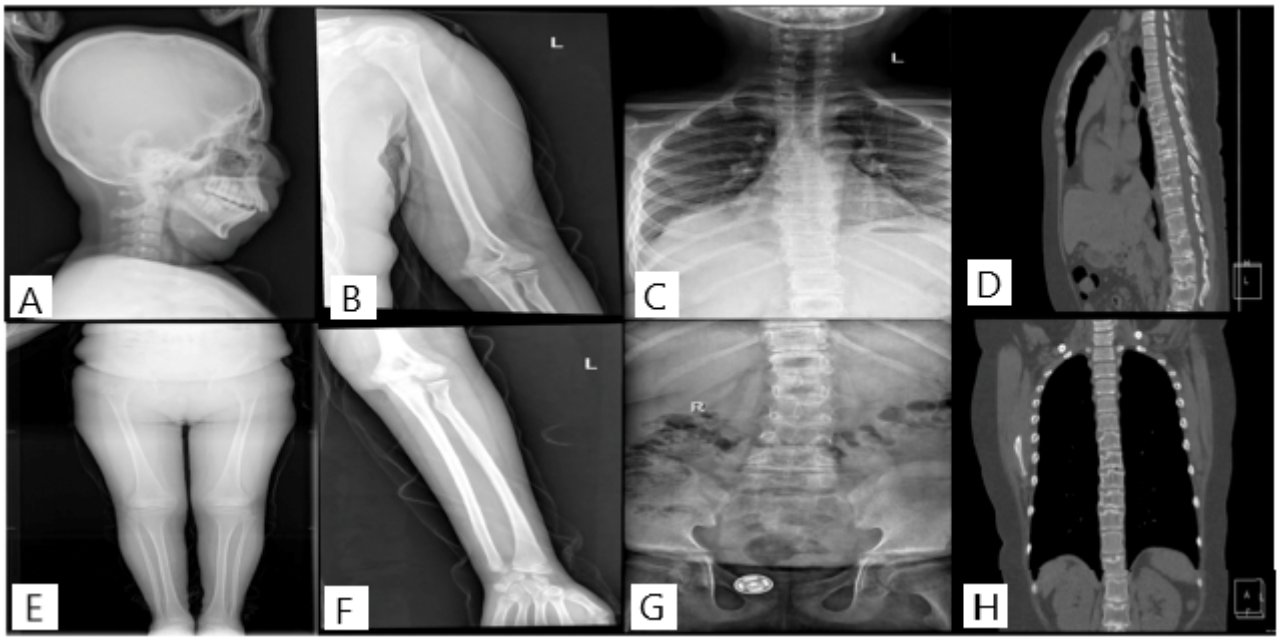

Figure 6. Radiographs and spine CT of child age 12 years with *MBTPS1*-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes

A, B, E, F. No obvious abnormalities in long bones or lateral skull radiograph

C, G. Radiographs show dysplasia of multiple thoracolumbar vertebrae and scoliosis.

D, H. Spine CT shows rough edges of vertebra, end plate bone defects, and narrow intervertebral spaces.

Reproduced with permission from Yuan et al [2023]

Table 1. Molecular Genetic Testing Used in *MBTPS1*-Related Spondyloepimetaphyseal Dysplasia with Elevated Lysosomal Enzymes

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
MBTPS1	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

MBTPS1-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes (*MBTPS1*-SEMD) is characterized by postnatal-onset short stature, pectus deformity, kyphosis and/or scoliosis, hernia, protruding abdomen, cataract(s), developmental delay, and dysmorphic facial features, in combination with elevated lysosomal hydrolase enzyme levels in plasma. Additional features can include waddling or staggering gait, craniosynostosis, and seizures. To date six individuals with *MBTPS1*-SEMD from six families have been reported [Kondo et al 2018, Carvalho et al 2020, Meyer et al 2020, Alotaibi et al 2022, Chen et al 2023, Yuan et al 2023]. Three additional affected individuals are known to the authors. The features in Table 2 and the following description are based on published reports.

Table 2. *MBTPS1*-Related Spondyloepimetaphyseal Dysplasia with Elevated Lysosomal Enzymes: Frequency of Select Features

Feature		Proportion of Persons w/Feature	Comments
Short stature		6/6	
Chest deformity		6/6	Pectus carinatum, pectus excavatum
Kyphosis &/or scoliosis		5/6	
Hernia / protruding abdomen		6/6	
Cataract		5/6	
Developmental delay		5/6	Incl gross motor & speech delays
Dysmorphic facies	**Prominent forehead**	5/6	
	Prominent cheek bones	5/6	
	Retromicrognathia	6/6	
	Wide mouth	5/6	
	Large ears	6/6	

Alotaibi et al [2022], Yuan et al [2023]

Growth deficiency. Postnatal-onset short stature was present in all reported individuals and was typically identified by age three years. Two individuals were treated with growth hormone therapy. One individual started treatment at age three years and discontinued after one year without improvement in growth velocity [Kondo et al 2018]. In a second individual with normal insulin-like growth factor 1 (IGF-1), recombinant intravenous growth hormone (rhGH) of 0.15-0.2 IU/kg per day was started at age three years; after three years of rhGH therapy, the height increased from 5.3 standard deviations (SD) below the mean (before treatment) to 3.96 SD below the mean (after three years of treatment) [Chen et al 2022]. The range of severity of growth deficiency following treatment with growth hormone was from 2.9 to 5.3 SD below the mean.

Musculoskeletal manifestations. Chest deformity including pectus carinatum, pectus excavatum, or unspecified sternal malformation was reported in all individuals. Kyphoscoliosis or scoliosis was present in all individuals. Reduced bone density was evident in all individuals. Anterolisthesis of L5 on S1 has been described in one individual [Kondo et al 2018].

Hip dislocation with coxa vara was reported in one individual [Alotaibi et al 2022]. Waddling or staggering gait was reported in two individuals [Alotaibi et al 2022, Yuan et al 2023].

Craniosynostosis was identified in two individuals [Carvalho et al 2020], including one individual originally reported by Kondo et al [2018] with craniosynostosis identified after images were reevaluated by the authors.

Short neck and rhizomelia were reported in one individual [Carvalho et al 2020]; brachydactyly, genu valgum, valgus tibial bowing, and pes cavus were reported in one individual [Alotaibi et al 2022]; pes valgus and prominent sandal grooves were reported in one individual [Meyer et al 2020] (see Figure 2). Hyperextended fingers were reported in one individual [Yuan et al 2023].

Hernia or protruding abdomen were reported in all individuals. Bilateral inguinal hernia was reported in two individuals [Kondo et al 2018] and unilateral inguinal hernia with protruding navel in one individual [Meyer et al 2020]. Three individuals had protruding abdomen [Carvalho et al 2020, Alotaibi et al 2022, Chen et al 2022].

Cataracts were common. Two individuals had congenital lamellar cataract, with surgical lens removed at age ten months [Carvalho et al 2020] and age 35 months [Chen et al 2022]. One individual had punctiform opacities of the lens identified at age 11 years, keratoconus that was treated at age 11 years, and anterior and posterior subcapsular cataract that was detected at age 18 years [Meyer et al 2020].

Developmental delays. Most individuals had gross motor delays. Three individuals started walking at age 15 months, 24 months, and 36 months [Carvalho et al 2020, Meyer et al 2020, Alotaibi et al 2022]. Three individuals had speech and language delay [Meyer et al 2020, Alotaibi et al 2022]; one of these children had first sounds at age 21 months and feeding problems with poor weight gain managed with gastrostomy tube feeding for several months [Meyer et al 2020]. One individual was reported to have expressive language delay, with first words spoken at age 26 months [Carvalho et al 2020].

Intelligence is normal in the majority of individuals. One individual was reported with below-average intelligence [Alotaibi et al 2022], and a second individual had mild intellectual disability with an IQ of 57 [Yuan et al 2023].

Dysmorphic features. Characteristic dysmorphic features were present in the majority of individuals, including prominent forehead, prominent cheekbones, retromicrognathia, wide mouth, and large, prominent ears (see Figure 1).

Other features

- Generalized seizure activity (1 individual) [Carvalho et al 2020]
- Accumulation of fat on the chest and abdomen (1 individual) [Yuan et al 2023]
- Epicanthal folds and high nasal bridge (1 individual) [Yuan et al 2023]

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

The prevalence of this condition is unknown. To date, only six individuals from six families have been reported in literature. There are an additional three individuals known to the authors, including an affected fetus.

Genetically Related (Allelic) Disorders

Cataract, alopecia, oral mucosal disorders, and psoriasis-like (CAOP) syndrome. Early-onset bilateral cataracts, generalized nonscarring alopecia, oral mucosal disorder (red and swollen gums), and severe psoriasiform skin lesions (affecting the scalp, face, inguinal region, buttocks, and lower extremities) were described in two individuals with compound heterozygous pathogenic variants in *MBTPS1* including one stop loss variant [Chen et al 2022]. It is unclear if lysosomal hydrolase enzymes are elevated in CAOP syndrome; in one of the reported individuals, elevated hydrolases were not detected.

HyperCKemia and focal myoedema were reported in one individual with a heterozygous *MBTPS1* pathogenic variant [Schweitzer et al 2019].

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of *MBTPS1*-Related Spondyloepimetaphyseal Dysplasia with Elevated Lysosomal Enzymes

Gene	Disorder	MOI	Selected Features of Disorder	
			Clinical	Radiographic
Genetically heterogeneous [1]	Silver-Russell syndrome	See footnote 1.	• Growth deficiency • Relative macrocephaly • Frontal bossing or prominent forehead • Body asymmetry	
ARSE	Chondrodysplasia punctata 1, X-linked	XL	• Brachytelephalangy • Nasomaxillary hypoplasia • Postnatal short stature	• Stippled epiphyses • Calcifications • Vertebral abnormalities
COL2A1	Spondyloepiphyseal dysplasia congenita (SEDC), *COL2A1*-related (See Type II Collagen Disorders Overview.)	AD (AR) [2]	• Severe disproportionate short stature, short extremities • Hypertelorism, flat profile, Pierre Robin sequence • Myopia & hearing loss	• Delayed/poor ossification of vertebrae & pubic bones • Short long bones w/ hypoplastic epiphyses • ↑ risk for cervical instability & spinal cord compression

Table 3. continued from previous page.

Gene	Disorder	MOI	Selected Features of Disorder	
			Clinical	Radiographic
	Spondyloperipheral dysplasia, *COL2A1*-related (See Type II Collagen Disorders Overview.)	AD	• Mild-to-moderate disproportionate short stature & short extremities • Brachydactyly type E, short ulnae, variable clubfeet, cleft palate • Myopia & hearing loss	• Ovoid vertebra • Delayed ossification of pubic bones • Flattened & irregular epiphyses in long bones • Premature hip arthrosis causes joint pain.
	Kniest dysplasia, *COL2A1*-related (See Type II Collagen Disorders Overview.)	AD	• Severe disproportionate short stature, short neck, short thorax, short extremities • Myopia, vitreous abnormalities, & retinal detachment	• Platyspondyly w/ anterior wedging & coronal clefting of lumbar vertebral bodies • Delayed ossification in distal femoral & proximal tibial epiphyseal ossification centers • Short long bones w/ large metaphyses & epiphyses
	Spondyloepimetaphyseal dysplasia, *COL2A1*-related (See Type II Collagen Disorders Overview.)	AD	Infants initially present w/same findings as those w/SEDC.	Metaphyseal flaring becomes evident in 1st yr of life.
EBP	Chondrodysplasia punctata 2, X-linked	XL	• Growth deficiency • Frontal bossing; depressed nasal bridge; sparse eyebrows & lashes, often asymmetric • Rhizomelia • Scoliosis • Abnormalities of skin, hair, & nails; ocular anomaly	Stippling involving epiphyses of long bones & vertebrae, trachea, & distal ends of ribs
GALNS	Mucopolysaccharidosis type IVA	AR	• Marked disproportionate short stature w/short trunk • Ulnar deviation of wrists • Pectus carinatum & flaring of lower rib cage • Gibbus, kyphosis, & scoliosis • Genu valgum • Hypermobile joints • Waddling gait w/frequent falls	• Odontoid hypoplasia w/subsequent cervical instability • Short ulnas & delayed bone maturation • Short metacarpals • Flared iliac wings, flattening of femoral epiphyses, & coxa valga
GLB1	Mucopolysaccharidosis type IVB (MPS IVB) (See *GLB1*-Related Disorders.)	AR	• Short stature (below 15th centile in adults) • Kyphoscoliosis • Joint laxity	• Axial & appendicular dysostosis multiplex • Platyspondyly • Odontoid hypoplasia • Coxa/genu valga

Table 3. continued from previous page.

Gene	Disorder	MOI	Selected Features of Disorder	
			Clinical	Radiographic
GNPTAB	Mucolipidosis II (See *GNPTAB*-Related Disorders.)	AR	In neonatal period: • Small to low-normal anthropometric measurements for gestational age • Restricted range of passive motion in shoulders • Flat face, shallow orbits, depressed nasal bridge • Thick skin w/wax-like texture • Variable musculoskeletal findings Note: Activity of multiple lysosomal hydrolases is ↑ in plasma, dried blood, & other body fluids.	Severe dysostosis multiplex
GNPTG	Mucolipidosis III gamma	AR	• Growth rate deceleration • Joint stiffness of fingers, shoulders, & hips • Gradual mild coarsening of facial features • Genu valgum • Spinal deformities incl scoliosis & hyperlordosis • No organomegaly Note: Activity of nearly all lysosomal hydrolases is up to 10x higher than normal in plasma, dried blood, & other body fluids.	• Mild-to-moderate dysostosis multiplex • Hypoplastic iliac bones w/flared iliac wings • Shallow & irregular acetabula & moderate-to-severe dysplasia of proximal femoral epiphyses giving rise to coxa valga
TRAPPC2	X-linked spondyloepiphyseal dysplasia tarda (SED-XL), *TRAPPC2*-related	XL	• Disproportionate short stature in adolescence or adulthood w/short trunk & barrel-shaped chest. • Short neck, dorsal kyphosis, scoliosis, & lumbar hyperlordosis may be evident by puberty. • Early-onset osteoarthritis	• Multiple epiphyseal abnormalities • Platyspondyly; characteristic superior & inferior "humping" on lateral radiograph • Hypoplastic odontoid process • Short femoral necks • Coxa vara

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; MOI = mode of inheritance; SEDC = spondyloepiphyseal dysplasia congenita; XL = X-linked

1. Hypomethylation of the imprinted control region 1 (ICR1) at 11p15.5 causes Silver-Russell syndrome (SRS) in 35%-50% of individuals; maternal uniparental disomy causes SRS in 7%-10% of individuals. A small number of affected individuals have duplications, deletions, or translocations involving the imprinting centers at 11p15.5 or duplications, deletions, or translocations involving chromosome 7. Rarely, SRS is caused by pathogenic variants in *CDKN1C*, *IGF2*, *PLAG1*, or *HMGA2*. Accurate assessment of SRS recurrence risk requires identification of the causative genetic mechanism in the proband.

2. Type II collagen disorders are inherited in an autosomal dominant manner. However, rare instances of autosomal recessive inheritance in spondyloepiphyseal dysplasia congenita have been reported.

Management

No clinical practice guidelines for *MBTPS1*-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes (*MBTPS1*-SEMD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *MBTPS1*-SEMD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *MBTPS1*-Related Spondyloepimetaphyseal Dysplasia with Elevated Lysosomal Enzymes: Recommended Evaluations Following Initial Diagnosis

System/Concerns	Evaluation	Comment
Growth/Nutrition	• Assess growth. • Gastroenterology / nutrition / feeding team eval	Consider eval for gastrostomy tube placement in those w/feeding issues & poor weight gain for height in early childhood
Musculoskeletal	• Skeletal survey • Orthopedist / PT & OT eval • DXA scan	Assess for skeletal manifestations incl chest deformity, spine abnormalities, hip dysplasia, & craniosynostosis w/additional imaging as needed
Hernia	General surgery eval in those w/inguinal hernia	
Eyes	Ophthalmologic eval to assess for cataract	
Development	Developmental eval inclu gross & fine motor, speech & language, cognitive & performance, & activities of daily living	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *MBTPS1*-SEMD to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support

DXA = dual x-ray absorptiometry; *MBTPS1*-SEMD = *MBTPS1*-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. *MBTPS1*-Related Spondyloepimetaphyseal Dysplasia with Elevated Lysosomal Enzymes: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Growth deficiency	• GH therapy can be tried, but outcome is uncertain. • It is unknown if GH therapy can lead to worsening of disproportionate growth in those w/spinal dysplasia.	GH therapy improved growth velocity in 1 person, [1] there was no benefit in another person. [2]

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Kyphoscoliosis/ Scoliosis	• Operative mgmt may be warranted in those w/neurologic manifestations. • In those w/o neurologic compromise, procedures such as vertebroplasty & kyphoplasty may be considered for vertebral augmentation.	Operative mgmt may be indicated in those who have failed conservative therapy, experience intractable pain, have an onset of neurologic changes, or have persistent progression despite bracing.
Reduced bone density	Vitamin D & calcium may be used as a supplement for reduced bone density.	
Hip dysplasia	Treatment per orthopedist	
Craniosynostosis	Treatment per craniofacial specialist	
Hernia	Surgical repair per surgeon &/or gastroenterologist	
Cataract	Surgical removal of cataract per ophthalmologist	
Developmental delay	Physical therapy	To maximize mobility & reduce risk for later-onset orthopedic complications (e.g., scoliosis)
	Developmental & educational support incl: • Early intervention programs • Early childhood education • Early & periodic screening, diagnosis, & treatment (EPSDT)	

GH = growth hormone
1. Chen et al [2023]
2. Kondo et al [2018]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *MBTPS1*-Related Spondyloepimetaphyseal Dysplasia with Elevated Lysosomal Enzymes: Recommended Surveillance

System/Concern	Evaluation	Frequency
Short stature	Growth assessment	Annually
Kyphosis / Scoliosis / Other skeletal manifestations	Orthopedic eval	
Hernia	Clinical assessment for hernia	As needed
Cataract	Ophthalmologic eval	Annually
Developmental delay	Monitor developmental progress & educational needs	

Agents/Circumstances to Avoid

In children with significant kyphoscoliosis, sports that place stress on the spine (e.g., heavy lifting, weight-bearing exercises) should be avoided.

Evaluation of Relatives at Risk

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

Pregnancy Management

No pregnancies have been reported in individuals with *MBTPS*-SEMD. Pregnancy and delivery may be complicated in individuals with significant short stature and skeletal dysplasia; delivery by cesarean section may be necessary.

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

MBTPS1-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes (*MBTPS1*-SEMD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *MBTPS1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *MBTPS1* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *MBTPS1* pathogenic variant, each sib of an affected individual has at conception 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with *MBTPS1*-SEMD are obligate heterozygotes (carriers) for a pathogenic variant in *MBTPS1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *MBTPS1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *MBTPS1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *MBTPS1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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**
  www.hgfound.org
- **MAGIC Foundation**
  Phone: 800-362-4423
  Email: contactus@magicfoundation.org
  www.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. MBTPS1-Related Spondyloepimetaphyseal Dysplasia with Elevated Lysosomal Enzymes: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MBTPS1	16q23.3-q24.1	Membrane-bound transcription factor site-1 protease	MBTPS1 @ LOVD	MBTPS1	MBTPS1

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 MBTPS1-Related Spondyloepimetaphyseal Dysplasia with Elevated Lysosomal Enzymes (View All in OMIM)

603355	MEMBRANE-BOUND TRANSCRIPTION FACTOR PROTEASE, SITE 1; MBTPS1
618392	SPONDYLOEPIPHYSEAL DYSPLASIA, KONDO-FU TYPE; SEDKF

Molecular Pathogenesis

Membrane-bound transcription factor site-1 protease (MBTPS1; also known as S1P) is a serine protease located in the Golgi. MBTPS1 has been shown to regulate lipogenesis, endoplasmic reticulum (ER) function, and lysosome biogenesis in mice and cultured cells [Kondo et al 2018]. Defective MBTPS1 function impairs activation of the ER stress transducer BBF2H7, leading to ER retention of collagen in chondrocytes. MBTPS1 deficiency also causes abnormal secretion of lysosomal enzymes due to partial impairment of mannose-6-phosphate-dependent delivery to lysosomes. Collectively, these abnormalities lead to apoptosis of chondrocytes and lysosomal enzyme-mediated degradation of the bone matrix.

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

Hua Wang, MD, PhD, is a clinical geneticist. Her research interests are skeletal dysplasia and lysosomal storage disorders. She runs a skeletal dysplasia clinic and diagnoses and manages individuals with lysosomal storage disease as well as other genetic disorders.

Andrea Wierenga, PhD, is a clinical biochemical geneticist. Her interest is exploring biochemical aspects of rare diseases and research associated with biochemical disorders.

Sandeep Prabhu, MD, is a pediatric radiologist with interest and expertise in skeletal dysplasia.

Klaas Wierenga, MD, is a clinical geneticist and medical biochemical geneticist. His research interest is rare disease diagnostics, with special interest in clinical homozygosity mapping.

Klaas Wierenga, MD, Hua Wang, MD, PhD, Lijun Xia, MD (lijun-xia@omrf.org), and Patrick Gaffney, MD (patrick-gaffney@omrf.org), are actively involved in clinical research regarding individuals with *MBTPS1*-related spondyloepimetaphyseal dysplasia with elevated lysosomal enzymes (*MBTPS1*-SEMD). They would be happy to communicate with persons who have any questions regarding diagnosis of *MBTPS1*-SEMD or other considerations.

Contact the previously mentioned physicians and researchers to inquire about review of *MBTPS1* variants of uncertain significance.

***MBTPS1*-Related Disorders Research Group**
Phone: 405-271-6673
Web: omrf.org/mbtps-related-disorders-research-group

This research group aims to increase the understanding of *MBTPS1*-SEMD. Physicians and families interested in obtaining more information are encouraged to reach out.

Acknowledgments

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- 30 November 2023 (sw) Review posted live
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