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NLM Citation: Bhavani GSL, Singh S, Girisha KM. *EXOC6B*-Related Spondyloepimetaphyseal Dysplasia with Joint Laxity. 2023 May 25. 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/

EXOC6B-Related Spondyloepimetaphyseal Dysplasia with Joint Laxity

Synonym: Spondyloepimetaphyseal Dysplasia with Joint Laxity, Type 3 (SEMDJL3)

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Created: May 25, 2023.

Summary

Clinical characteristics

EXOC6B-related spondyloepimetaphyseal dysplasia with joint laxity (*EXOC6B*-SEMD-JL) is characterized by multiple joint dislocations, joint laxity, genu valgum, short stature, and skeletal dysplasia. Joint dislocations of the hips and knees are present at birth in all individuals reported to date. Dislocations can also occur at the elbows, wrists, ankles, and patellae. Growth deficiency develops postnatally. Short neck, scoliosis, kyphosis, and hyperlordosis are reported. The fingers are slender (leptodactyly). Radiographic manifestations include delayed carpal/tarsal bone ossification, gracile short tubular bones, metaphyseal and epiphyseal dysplasia, slender ribs, and spondylar dysplasia (irregular vertebral end plates, narrow interpedicular distance of the lumbar spine, and modest platyspondyly) with age-dependent evolution.

Diagnosis/testing

The diagnosis of *EXOC6B*-SEMD-JL is established in a proband with characteristic clinical and radiographic features and biallelic pathogenic variants in *EXOC6B* identified by molecular genetic testing.

Management

Treatment of manifestations: Surgical interventions for joint dislocations to improve mobility; wheelchair and walking aids as needed; physical therapy and orthopedic interventions as needed for scoliosis and kyphosis.

Surveillance: Annual assessment of joints by a rheumatologist or orthopedic surgeon; annual clinical and radiographic assessment for scoliosis and/or kyphosis.

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Genetic counseling

EXOC6B-SEMD-JL is inherited in autosomal recessive manner. If both parents are known to be heterozygous for an *EXOC6B* 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 *EXOC6B* 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

EXOC6B-related spondyloepimetaphyseal dysplasia with joint laxity (*EXOC6B*-SEMD-JL) **should be suspected** in probands with the following clinical, imaging, and family history findings.

Clinical findings

- Congenital dislocations of the hips and knees; may also affect elbows, wrists, and/or ankles
- Joint laxity affecting all joints and most evident at the wrists and fingers
- Postnatal-onset short stature
- Slender fingers (leptodactyly)
- Genu valgum
- Pes planus

Imaging findings

- Delayed carpal/tarsal bone ossification
- Slender/gracile short tubular bones (leptodactyly)
- Metaphyseal dysplasia. Irregular metaphyses with short sclerotic striations at the distal radius, distal ulna, distal femora, and proximal tibia
- Epiphyseal dysplasia (generalized). Carpal and tarsal bones are usually smaller and irregular; epiphyses of the long bones appear flat and small.
- Slender ribs
- Irregular vertebral end plates and modest platyspondyly (Platyspondyly is seen only in younger individuals and becomes less conspicuous with age; even tall vertebral bodies are seen in older affected individuals.)
- Narrow interpedicular distance of the lumbar vertebrae
- Thoracolumbar scoliosis, kyphosis, and/or hyperlordosis

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 *EXOC6B*-SEMD-JL **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *EXOC6B* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic, and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *EXOC6B* variants of

uncertain significance (or of one known *EXOC6B* pathogenic variant and one *EXOC6B* 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) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. 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 *EXOC6B*-SEMD-JL has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the clinical and imaging findings suggest the diagnosis of *EXOC6B*-SEMD-JL, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *EXOC6B* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. 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.
- **A skeletal dysplasia multigene panel** that includes *EXOC6B* and other genes of interest (see Differential Diagnosis) may be considered 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.

Option 2

When the diagnosis of *EXOC6B*-SEMD-JL has not been considered because an individual has atypical phenotypic features, **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.

Table 1. Molecular Genetic Testing Used in *EXOC6B*-Related Spondyloepimetaphyseal Dysplasia with Joint Laxity

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
EXOC6B	Sequence analysis [3]	3/5 families [4]
	Gene-targeted deletion/duplication analysis [5]	2/5 families [6]

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 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.
4. Girisha et al [2016]; Simsek-Kiper et al [2022]; Authors, personal communication
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.
6. An intragenic deletion of *EXOC6B* involving exons 9-20 and a second deletion involving exon 20 were reported in one individual each with *EXOC6B*-SEMD-JL [Campos-Xavier et al 2018, Simsek-Kiper et al 2022]. Copy number analysis from exome sequencing data can also detect these variants.

Clinical Characteristics

Clinical Description

EXOC6B-related spondyloepimetaphyseal dysplasia with joint laxity (*EXOC6B*-SEMD-JL) is characterized by multiple joint dislocations, joint laxity, short stature, scoliosis, kyphosis, and skeletal dysplasia (delayed carpal/tarsal bone ossification, leptodactyly, slender ribs, and vertebral anomalies). To date, seven individuals from five unrelated families have been identified with biallelic pathogenic variants in *EXOC6B* [Girisha et al 2016; Campos-Xavier et al 2018; Simsek-Kiper et al 2022; Authors, personal communication]. Most individuals have normal intellect, though developmental delay and hydrocephalus were noted in one individual [Simsek-Kiper et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *EXOC6B*-Related Spondyloepimetaphyseal Dysplasia with Joint Laxity: Frequency of Select Features

Feature		Proportion of Persons w/ Feature	Comment
Clinical manifestations	Joint dislocations	7/7	Primarily hips & knees
	Joint laxity	7/7	
	Short stature	7/7	Postnatal onset
	Slender fingers	7/7	
	Genu valgum	6/7	
	Pes planus	4/7	
	Spine manifestations	6/7	Scoliosis, kyphosis, short neck, &/or hyperlordosis
	Barrel-shaped chest	2/7	

Table 2. continued from previous page.

Feature		Proportion of Persons w/ Feature	Comment
Radiographic findings	Delayed carpal bone ossifications	7/7	
	Gracile, short tubular bones (leptodactyly)	6/7	
	Metaphyseal dysplasia	6/7	
	Epiphyseal dysplasia	6/7	
	Slender ribs	4/7	
	Irregular vertebral end plates	3/7	
	Narrow interpedicular distance of lumbar vertebrae	3/7	
	Platyspondyly	2/7	

Joint manifestations. All reported individuals have joint dislocations at birth; hip and knee joints are affected in all individuals. Other joints that are often dislocated include elbows, wrists, and ankles. The patella can also be dislocated. All affected individuals demonstrate joint laxity, most evident at the wrists and fingers.

Short stature. Growth deficiency develops postnatally; spinal deformities and dislocation of the hip joints may contribute to reduced height.

Hands and feet. Slender fingers are reported in all individuals. Pes planus may be present. Radiographs show slender, short tubular bones in all individuals. The wrists and ankle joints show small, irregular, and disorganized carpal bones with abnormal/delayed carpal bone ossification.

Spine manifestations include scoliosis (6 individuals), kyphosis (4 individuals), and hyperlordosis (2 individuals). Short neck was reported in four individuals. Radiographs show irregular vertebral end plates, narrow interpedicular distance of the lumbar vertebrae, and platyspondyly that is evident only in younger individuals.

Facial features. There are no specific characteristic facial features. However, broad forehead (2 individuals), small chin (2 individuals), and triangular face have been noted in some individuals.

Other

- Soft skin
- Developmental delay (1 individual) [Evers et al 2014]
- Hydrocephalus (1 individual)

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

Seven individuals from five unrelated families with *EXOC6B*-SEMD-JL have been reported to date.

Genetically Related (Allelic) Disorders

Intellectual disability has been reported in individuals with genetic alterations (intragenic pathogenic variants, contiguous gene deletions, and translocations) involving *EXOC6B* [Evers et al 2014]. No skeletal abnormalities

are described in these individuals. Currently there is insufficient evidence to suggest a causal relationship of haploinsufficiency of *EXOC6B* and intellectual disability.

Differential Diagnosis

Table 3. Common Conditions with Multiple Joint Problems (Laxity, Dislocations, Restriction of Joint Movement) in the Differential Diagnosis of *EXOC6B*-Related Spondyloepimetaphyseal Dysplasia with Joint Laxity

Gene	Disorder [1]	MOI	Clinical Findings	Imaging Findings
B3GALT6	SEMD-JL (Beighton type), *B3GALT6*-related (OMIM 271640)	AR	• Prenatal-onset short stature • Facial dysmorphism (oval face, prominent forehead, prominent eyes, blue sclera, micrognathia, cleft palate) • Progressive kyphoscoliosis & joint dislocation	• Progressive kyphoscoliosis • Ovoid vertebral bodies • Severe platyspondyly • Short, flared iliac wings • Radioulnar dislocation
B3GAT3	Multiple joint dislocations, short stature, craniofacial dysmorphisms, & skeletal dysplasia ± heart defects, *B3GAT3*-related (OMIM 245600)	AR	• Short stature • Brachycephaly, prominent forehead • Multiple joint dislocations • Cardiac anomalies	• Scoliosis • Occasionally modest platyspondyly • Dislocation of radioulnar & interphalangeal joints • Broad ilia • Long phalanges w/relatively short metacarpals • Occasionally generalized osteoporosis
B4GALT7	Ehlers-Danlos syndrome, spondylodysplastic type 1 (EDSSPD1), *B4GALT7*-related (OMIM 130070)	AR	• Short stature • Broad, flat forehead • Joint laxity & dislocations • Long, slender fingers & toes • Loose elastic skin	• Scoliosis • Large joint dislocation • Radioulnar synostosis
CANT1	Desbuquois dysplasia, *CANT1*-related (OMIM 251450)	AR	• Prenatal-onset short stature • Midface hypoplasia • Joint dislocations	• Occasionally, multiple coronal clefts of vertebral bodies • Advanced carpal ossification • Monkey wrench femora • Hyperphalangy of index finger
CHST3	Chondrodysplasia w/ congenital joint dislocations, *CHST3*-related (See *CHST3*-Related Skeletal Dysplasia.)	AR	• Short stature • Joint dislocations &/or restriction of joint movement • Clubfeet • Kyphoscoliosis	• Multiple coronal clefts of vertebral bodies • Increase in interpedicular distance from T12 to L1 or L2 • Bifid distal humerus • Accessory carpal ossification centers
GZF1	Joint laxity, short stature, & myopia (OMIM 617662)	AR	• Short stature • Severe myopia • Joint dislocation & laxity	• Osteopenia • Progressive kyphoscoliosis

Table 3. continued from previous page.

Gene	Disorder [1]	MOI	Clinical Findings	Imaging Findings
KIF22	SEMD-JL (Hall type or leptodactylic type), *KIF22*-related (OMIM 603546)	AD	• Short stature • Knee/hip joint dislocation • Midface hypoplasia • Joint laxity • Genu valgum • Velvety skin • Hypotonia	• Progressive scoliosis • Vertebral dysplasia (modest platyspondyly in younger persons) • Epimetaphyseal dysplasia (small, flat epiphyses & irregular metaphyses w/longitudinal striations) • Gracile, short tubular bones
NIN	SEMD-JL (leptodactyly-like phenotype) [2]	AR	• Microcephaly • Primordial short stature • Flat facial features • Joint laxity • Joint dislocation • Genu valgum • Pes cavus	• Scoliosis • Squared vertebral bodies • Irregular vertebral end plates • Slender, short tubular bones • Metaphyseal striations
XYLT1	Baratela-Scott syndrome, *XYLT1*-related (formerly Desbuquois dysplasia type 2) (OMIM 615777)	AR	• Prenatal-onset short stature • Midface hypoplasia • Joint dislocations	• Multiple coronal clefts of vertebral bodies • Advanced carpal ossification

AD = autosomal dominant; AR = autosomal recessive; SEMD-JL = spondyloepimetaphyseal dysplasia with joint laxity; MOI = mode of inheritance

1. Disorder names are from the Nosology of Genetic Skeletal Disorders: 2023 Revision [Unger et al 2023].

2. This condition is not well characterized; only one family has been reported to date [Grosch et al 2013].

Management

No clinical practice guidelines for *EXOC6B*-related spondyloepimetaphyseal dysplasia with joint laxity (*EXOC6B*-SEMD-JL) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *EXOC6B*-SEMD-JL, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *EXOC6B*-Related Spondyloepimetaphyseal Dysplasia with Joint Laxity: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Musculoskeletal	• Complete skeletal survey • Eval by orthopedic surgeon & PT to assess joint range of motion	Orthopedic interventions may be needed for joint dislocations.
Cardiovascular	Echocardiography	For routine cardiac eval
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *EXOC6B*-SEMD-JL to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

EXOC6B-SEMD-JL = *EXOC6B*-related spondyloepimetaphyseal dysplasia with joint laxity; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *EXOC6B*-SEMD-JL. 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. *EXOC6B*-Related Spondyloepimetaphyseal Dysplasia with Joint Laxity: Treatment of Manifestations

Manifestation/Concern	Treatment
Joint manifestations	• Surgical interventions to remedy joint dislocations & improve mobility • Wheelchair &/or walking aids may be necessary.
Scoliosis/Kyphosis	Physical therapy & orthopedic interventions

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. *EXOC6B*-Related Spondyloepimetaphyseal Dysplasia with Joint Laxity: Recommended Surveillance

System/Concern	Evaluation	Frequency
Joint manifestations	Assessment of joints by rheumatologist or orthopedic surgeon	Annually
Scoliosis/Kyphosis	Clinical & radiographic assessment	

Agents/Circumstances to Avoid

Activities with a high impact on joints that may increase the risk of dislocation should be avoided.

Obesity should be avoided to reduce the negative impact on joints.

Evaluation of Relatives at Risk

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

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

EXOC6B-related spondyloepimetaphyseal dysplasia with joint laxity (*EXOC6B*-SEMD-JL) 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 *EXOC6B* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *EXOC6B* 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 *EXOC6B* 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. Unless an affected individual's reproductive partner also has *EXOC6B*-SEMD-JL or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *EXOC6B*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *EXOC6B* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *EXOC6B* 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 *EXOC6B* 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.

- **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. EXOC6B-Related Spondyloepimetaphyseal Dysplasia with Joint Laxity: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
EXOC6B	2p13.2	Exocyst complex component 6B	EXOC6B	EXOC6B

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 EXOC6B-Related Spondyloepimetaphyseal Dysplasia with Joint Laxity (View All in OMIM)

607880	EXOCYST COMPLEX COMPONENT 6B; EXOC6B
618395	SPONDYLOEPIMETAPHYSEAL DYSPLASIA WITH JOINT LAXITY, TYPE 3; SEMDJL3

Molecular Pathogenesis

EXOC6B encodes exocyst complex component 6B, which functions as a component of the exocyst complex. The exocyst complex facilitates transport and tethering of secretory vesicles from the Golgi complex to the plasma membrane prior to fusion during exocytosis [Mei & Guo 2018].

Mechanism of disease causation. Loss of function; however, the exact mechanism of disease causation is yet to be elucidated.

Chapter Notes

Author Notes

Dr Katta Mohan Girisha is interested in clinical care and research in individuals with skeletal dysplasia. He is also keen to identify more individuals with *EXOC6B*-related spondyloepimetaphyseal dysplasia with joint laxity (*EXOC6B*-SEMD-JL) to better characterize the phenotype and genotype.

Dr Katta Mohan Girisha (girish.katta@manipal.edu) and Dr Gandham SriLakshmi Bhavani (gsl.bhavani@manipal.edu) are actively involved in clinical research regarding *EXOC6B*-SEMD-JL. They would be happy to communicate with persons who have any questions regarding diagnosis of *EXOC6B*-SEMD-JL or other considerations.

Contact Dr Katta Mohan Girisha and Dr Gandham SriLakshmi Bhavani to inquire about review of *EXOC6B* variants of uncertain significance.

The authors of this chapter serve as moderators for the *EXOC6B* entry in the Human Disease Genes website series.

Acknowledgments

We acknowledge the financial support provided by CSIR-UGC NET Junior Research Fellowship awarded by Human Resource Development Group under Council of Scientific and Industrial Research: 08/028(0002)/2019-EMR-I (to Swati Singh).

Revision History

- 25 May 2023 (sw) Review posted live
- 20 March 2023 (kmg) Original submission

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